EXPERIMENTAL PHARMACOLOGY

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Illustrated with 56 Engravings and 7 Colored Plates

LEA & FEBIGER
PHILADELPHIA AND NEW YORK
1919

PREFACE.

In the preparation of this manual an attempt has been made to present experimental pharmacology in a brief, concise form, yet to give the student an adequate view of the field. In an elementary course where time is limited, it is neither possible nor necessary that each student or group of students should perform each separate experiment. However, every student should endeavor to see the work of all the others and be able to discuss these results, since a knowledge of the action of drugs is more important for the majority than the development of technical skill. On the other hand, it should be emphasized that the performance of as many experiments as possible is the best means of gaining a knowledge of drug action. An excellent method of correlating the student's knowledge is to compare the action of one drug with that of another. It is advised, therefore, that the exercises be studied in advance. The effect of each drug studied should be compared in detail with those of the preceding ones; especially should those drugs that are closely related, such as eserin, pilocarpin, strychnin, caffein, digitalis and epinephrin be studied together. It is only by such comparisons that a knowledge of drug action can be attained.

Laboratory work in pharmacology has as its aim three main objects:

1. To give a first-hand knowledge of the action of drugs, and to educate the student in the properties of living, circulating tissues. This knowledge can be obtained in no other way.
2. To illustrate the practice of pharmacologic investigations and the methods of procuring records and tracings. This enables the student better to understand literature and illustrations.
3. To develop the technic and methods of research, and the spirit of investigation.

This manual attempts to follow and illustrate the most important part of the text-book work. Sufficient experiments are given to demonstrate the chief actions of each drug. Some points are duplicated, but since each student does not perform every

exercise, there may be no actual repetition. Variations may be made as desired and demonstrations added. Those included in this outline are the accumulation of several years. No claim to originality is made. In fact an effort has been made to include those exercises which have been standardized by long and general use. In many instances we are not now able to credit the method outlined to its original source. Our chief attention has been devoted to selecting those of instructional value. However, in this connection it affords us pleasure to acknowledge our obligations to such eminent authorities as Cushny, Sollmann, Greene, Stewart, Jackson, Becht, Hatcher, Hirschfelder, Hoskins, Dreyer and others.

H. McG.

CHICAGO, 1919.

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EXPERIMENTAL PHARMACOLOGY.

INTRODUCTION.

Definitions.—Pharmacology is the term used to include all knowledge pertaining to drugs and their actions. The term drug comes from the Anglo-Saxon word drugan = to dry. It was first used because dried plants in early times made up the whole materia medica. The term has grown with the extension of the materials used in medicine, and at present includes everything used as medicine.

Experimental pharmacology is a biological science, and as such is related to general biology, especially the subjects of:

Anatomy.
Physiology.
Pathology.
Chemistry and Biochemistry

The relation to biology is evident, since pharmacology is a study of the reactions of living material to changes in environment. These changes in environment are usually produced by drugs. It is related to anatomy, since this science is necessary as a foundation of the study of tissues. If we do not know the anatomy we cannot interpret physiological reactions. Physiology is the study of the functions of tissue and organisms, while pharmacology studies the same functions as modified by drugs. It is related to pathology, since the introduction of the drugs in itself is a pathological condition and many drugs readily create distinctly pathological states. For example, phosphorus may cause fatty degeneration of the liver, uranium salts may cause nephritis, etc. The relation to chemistry and to biochemistry is obvious. Drugs are chemicals, and the reactions of drugs with the organism is definitely a branch of organic or biologic chemistry. From this viewpoint pharmacology is a branch of applied organic chemistry.

The Subdivisions of Pharmacology are:

Materia medica.
Pharmacy.

Pharmacognosy.
Pharmacodynamics.
Therapeutics, including prescription writing and posology or dosage.
Toxicology.

These subdivisions are not sharply defined, and are for convenience only.

Materia Medica.—Materia medica treats of the source, constituents, physical and chemical characteristics and doses of drugs.

Pharmacy.—A study of the properties, preparation, compounding and dispensing of medicines.

Pharmacognosy.—Pharmacognosy, gross and microscopic, may be considered as a part of materia medica, and deals especially with the recognition of drugs and the study of crude materials. In the identification, the origin, the physical properties, chemical reactions, taste, odor, microscopic appearance, etc., may be considered.

Pharmacodynamics or Experimental Pharmacology.—The study of the action of drugs on the living organism includes clinical observations and experience as well as experimental work. Toxicology may be considered as a branch of pharmacodynamics. In the widest sense, pharmacodynamics is a study of reactions of living matter due to changes in environment.

Therapeutics.—The art and practice of treating abnormal states by any means that relieves pain, restores health or prolongs life. Any change in environment of an animal will have this effect, and comes under the term pharmacology in its broadest meaning.

Toxicology.—Toxicology deals with the symptoms, diagnosis, treatment and detection of poisons.

A poison may be defined arbitrarily as any substance which, when taken by mouth in doses of less than 50 gm. will injure health or cause death.

The distinction between foods; drugs and poisons is hard to make. A drug is anything that is used as a medicinal agent. Poison has been defined, but we should remember that there is no definition entirely satisfactory or generally accepted. A food is something that supplies energy to the body, does not injure the body when taken by mouth and will build up the tissue and repair waste.

Theories and Mode of Pharmacological Action.—The action of drugs may be physical or chemical.

Physical Actions.—Physical actions are those in which there is no chemical reaction between the drug and the tissues. The most important physical actions are:

1. The protective effect of oils, powders, gums, mucilage, collodions, and fixed dressings.

2. The osmotic effects (or salt action) of isotonic, hypotonic or hypertonic solutions.

3. The adsorptive or absorptive action of carbon, dyes, etc., infusorial earths and colloids generally.

Chemical Actions.—Some drugs exert a chemical reaction within the body. The nature of the action may be:

1. *Combination.*—(*a*) As the neutralization of an acid with a base, as when the hydrochloric acid of the stomach is neutralized by sodium bicarbonate; and the addition of HCl with NH_3.

(*b*) Such unknown reactions as selective affinity are probably chemical.

2. *Solution.*—The Meyton-Overton theory, which explains anesthesia as a solution of nervous material by ether, etc., is a chemical reaction. It should be remembered, however, that chemists hold different opinions regarding the nature of even the solution of salt in water, consequently the actual reaction in solutions may mean something different even to experts.

Results of Drug Action.—This is only a modification of normal functions or of the fundamental properties of living matter. The fundamental properties of life or living matter are:

1. Metabolism—anabolism and katabolism—which may include all digestive processes.

2. Excitability manifested by contractility, conduction, motility, secretion, etc.

3. Reproduction.

Drugs only modify these properties—they cannot create new functions.

Drugs can act then only by stimulation, depression or irritation of the normal processes. This shows clearly the relation of pharmacology to physiology.

By stimulation we mean an increase in the function of an organ or tissue.

By depression we mean a decrease in function.

In irritation the change is more anatomical than functional, and some of the signs of inflammation are present. These are redness, local increase in temperature, swelling and pain. There may be some changes in function which are of a secondary nature.

Drugs may also cause fatigue and paralysis, which are also modifications of function. The causes of fatigue may be due to:

1. The exhaustion of energy-yielding material.
2. The accumulation of waste products.

Experiments have shown that the order of the occurrence or ease of fatigue in the various tissues are:

1. Nerve center.
2. Nerve endings.
3. Muscle.
4. Nerve fibers.

Recovery from fatigue takes place with rest alone (*cf.* Paralysis).

Paralysis.—This may also be caused by a drug. It is due to a combination of the drug with the cell substance and recovery takes place only when the drug is removed (*cf.* Fatigue and Curare Action). The curare effect or action is a paralysis.

Paralysis may also be caused by anatomical changes or lesions. It is obvious that in some of these recovery cannot be expected. There are also many in which fatigue and paralysis cannot be separated or distinguished, so there are conditions in which there is ground for a legitimate difference of opinion. One must remember that when the problem of life itself is up for explanation, dogmatic assertions cannot always be made.

Elective Affinity or Selective Action.—When a drug is introduced into the body and it acts more on one tissue than another we say its action is selective. It would perhaps be better to say the tissue action is selective, *e. g.*, curare acts on the nerve-endings to striated muscle almost to the exclusion of other actions. Epinephrin acts on the endings of the sympathetic nerves. Many other drugs show this tendency to pick out a particular tissue and exert its action on it to the exclusion of others. Such actions are said to be selective.

General Protoplasm Actions and General Poisons.—If a drug acts on tissues generally without exhibiting an action on one more than another we say it has a general protoplasmic action, and if toxic it is a general protoplasmic poison.

Local, Remote and General Actions.—In many cases whether a drug exerts a local or remote action depends on the concentration and the mode of application.

Local Action.—Most drugs that are not absorbed have local action only, *e. g.*, demulcents and emollients; Bi and Ag salts; sprays in nose or throat; dusting powders and protectives act only where they are applied and the action is mainly of a physical nature.

By remote or indirect action we mean an action elicited in organs away from the site of application. Irritation of the skin, blisters

or cold applications in any region may influence the rate of the heart indirectly through the nervous system. Cerebral depressants in the same way, by lessening movement, lessen oxidation in the muscles. Atropin injected in the arm has no action locally but causes an increased heart-rate, because when carried in the circulation it paralyzes the vagus endings.

By general action we mean those actions that cannot be fixed on any one tissue, as the action of tonics, sedatives and the like.

Since all drugs may also be poisons, Loew's theory of the action and his classification of poisons may be given.

He classifies poisons as:

(*a*) *General.*—The general poisons are subdivided into:

1. Oxidizing:
   Ozone.
   Peroxides.
   Permanganates.
   Chromates.
   Hypochlorites, etc.

2. Catalytic: These do not undergo any apparent change themselves, but act on protoplasm. The volatile narcotics and enzymes are examples.

3. Salt-forming: Due to the amphoteric character of the protoplasm, some drugs, like acids, alkalies, tannins, etc., combine to form salts.

4. Substituting: These include all bodies which react with aldehydes and amins, forming substitution products. Such drugs are:
   Hydrazine.
   Phenol hydrazine.
   Anilin.
   Ammonia.
   Phenol.
   Hydrocyanic acid.
   Hydrogen sulphide and sulphites.

(*b*) *Special or Selective Poisons.*—These include toxins, antitoxins and the selective acting drugs, such as:
   Atropin.
   Strychnin.
   Curara.
   Eserin.
   Nicotin, etc.

Chemical Composition and Pharmacological Action.—All pharmacological actions are either chemical or physical. But all pharma-

cological action is exerted on and causes changes in the physical and chemical bases of life.

The physical bases of life are a viscid medium, a colloidal solution of proteids, salts, and water.

The Chemical Essentials of Life Are:

1. An energy-yielding substance.
2. Conditions suitable for their reaction and liberation of energy.
3. Proper temperature.
4. Alkalin reaction.
5. Ferments.
6. The presence of certain apparently essential chemical elements, *e. g.*, C,K,S, N, Cl, Fe, O, P, Mg.

With constant conditions we should expect a related action in a homologous chemical series, and in the paraffin series of alcohols, Baer gives the following ratio of toxicity for alcohols:

Methyl, 0.8.
Ethyl, 1.0.
Propyl, 2.0.
Butyl, 3.0.
Vinyl, 4.0.

As a matter of fact, however, such a relation is very rare, and while we might always expect a relation between the action of drugs and their chemical composition, there is more relation between their physical properties and the action. This is largely because we know only the elements of the chemistry of the body. At the same time we must remember that no one can even predict with certainty the action of the pure chemicals whose chemistry is well known. While we would expect the sulphides and the phosphates of the heavy metals to be alike in color and solubilities, there are many exceptions which can be determined by experiment only. With the animal organism the exceptions are more numerous than the conformities.

There is no law, therefore, known to exist between the chemistry of a drug and its reaction. Future work, however, will, we believe, ultimately establish such a law. Chemical pharmacology should therefore be studied as much as pharmacodynamics and offers more avenues of advance.

Conditions Modifying the Effects of Drugs.—These are:

1. *Habit.*—This usually lessens the effect to some extent.
2. *Size and Weight.*—Smaller persons require less than larger.
3. *Age.*—Young persons or animals require less than old.

The rule of dosage is as follows: The adult dose divided by the age plus twelve gives the dose for a child, *e. g.*, the dose for a child of

four years of a drug whose dose is 1 gram for an adult would be $\frac{4}{4} + 12 = \frac{1}{4}$ gram. This is Young's rule.

There are other rules, but this one is most used.

Opium and morphin are exceptions and the dose given should be smaller than the calculated dose.

4. *Women, chiefly because of size,* should get only four-fifths of the dose for men (idiosyncrasy is more often found in females).

5. *Temporary conditions, such as* meals, irritations and inflammatory conditions, neurasthenia, diarrhea and vomiting, pregnancy and lactation (drugs excreted in milk) must be considered in dosage.

6. *Time of administration:* Stomachics are best, given about thirty minutes before meals; cathartics, when convenient for patient and narcotics, at night.

7. *Idiosyncrasy:* Some persons have a peculiar susceptibility to drugs and react to a small dose in a manner that would indicate that many times the amount had been given. Congenital tolerance may be considered as an idiosyncrasy, but in this case, the organism is exceedingly resistant to the drug.

8. Tolerance differs from immunity in that there are no antibodies formed in tolerance. While there are in immunity it has not been shown that any chemical substances except proteins produce antibodies.[1]

9. Some drugs exert a cumulative effect due to irregularity of absorption—digitalis(?)—or slower excretion than absorption, which may occur with many drugs when kidney function is depressed.

10. *Synergists or Syngerism:* Mixtures of purgatives; mixtures of anesthetics; alcohol and acetonitril; narcotin and morphin, etc., act in some cases to accentuate the action of each other, and we get more than the additive action of the two. Such action is called synergistic. Note that it is more than an additive action.

11. *Antagonism.—Chemical or Therapeutic Incompatibility.*— Some drugs antagonize the action of others, *e. g.*, strychnin and chloroform, alcohol and caffein, pilocarpin and atropin. Drugs that antagonize each other and should not be administered at the same time.

12. *Pathological Conditions.*—Modify drug action. Antipyretics reduce the temperature in fever but not in the normal animal. Bromides lessen nervous irritability in epilepsy more than in normal states. Morphin in pain reduces sensitivity, but has less effect in health.

[1] For a review of the literature regarding morphin as a producer of antibodies, see Du Mez, Jour. Am. Med. Assn., 1919, lxxii, 1069.

The Method of Administration Modifies the Action of a Drug.—While we cannot in many cases correlate chemical composition and pharmacological action, we know that the concentration or mass action of chemistry holds true in the action of drugs in the body. It is for this reason that drugs react differently, depending on the method of application.

1. *Introduction of Drugs by Mouth.*—This is the usual method, and unless there is good reason to the contrary, should be the method used. But absorption is slower by this method than by most others, consequently the drug reaches the tissues slowly and may be oxidized or excreted almost as quickly as absorbed. This explains why drugs act in a relatively mild way when given by mouth.

2. *Introduction by Rectum.*—Drugs are sometimes given by this method to avoid action on the mouth and stomach and reflexes that might be exerted on the heart. They are absorbed more rapidly than when given by mouth, and the dose should be smaller. Usually it is one-half, though some give twice the dose, given by mouth.

3. *Hypodermic Injections.*—Drugs given in this way are very quickly absorbed. They are absorbed still more rapidly if given by intramuscular injection.

4. *Intramuscular Injection.*—Deep injection into the skeletal muscles, preferably the gluteus or deltoid. There is less pain and tenderness caused by drugs that are irritating when given deep into the muscles than when the injection is more superficial. Absorption by this method is also quicker than by any other method of administration except the intravenous method.

5. *Intravenous Injection.*—When drugs are injected into the vein they are applied directly to the point of action as quickly as the circulation can carry them. This was originally a laboratory method, but is much used clinically at present. It is too frequently used in clinical medicine and should not be used except when it is decidedly preferable to other methods. It is surprising how easily and how apparently non-irritating such caustic drugs as sodium carbonate may be injected intravenously, while if injected subcutaneously or intramuscularly they may produce sloughing. Strongly alkalin or acid-reacting solutions should never be given subcutaneously.

6. *Transfusion of Blood from the Artery* of one person to the vein of another, or from one animal to another, is much used in cases of hemorrhage, anemias, etc., and in investigative work.

7. *Inhalation.*—Inhalation is the usual method of giving general anesthetics. It depends on the fact that some drugs may be absorbed

from the lungs. Insufflation or inhalation is also used in nasal douches, etc. The advantages of inhalation is that the amount of the drug is readily controlled and removed. By the other methods if excess has been given it cannot be removed readily.

8. *Intraspinal Administration.*—By this method drugs are introduced into the spinal canal. The needle is introduced between the vertebræ, and the flow of fluid from the needle indicates when the needle is in place. In experimental work the fourth ventricle may also be entered. Care must be used in clinical work to keep the patient in a rigidly fixed position. As the reflex movement that anyone is likely to make when the needle enters the spinal canal may break the needle in the canal and this is a serious accident. It should never be tried on the human being without special instruction.

9. The local application of drugs needs no comment.

10. *Sublingual.*—Some drugs like nitroglycerin are in some cases best given by holding the tablet under the tongue. It dissolves readily and is absorbed very quickly.

11. *Insufflation.*—Powders are frequently insufflated or blown on to a surface. Boric acid, *e. g.*, is administered to the ear drum or other relatively inaccessible parts in this way.

The Fate of Drugs in the Body.—Drugs in the body may be oxidized and then excreted by any of the excretory organs. Catalytic drugs like ether are excreted unchanged either by the lungs, skin, kidneys or intestinal tract. Most drugs are oxidized to some degree. Others, like the oxalates, are combined with calcium, and still others, like the saline cathartics, may be excreted in great part unchanged. In studying what the action of the drug is on the body, the fate of the drug or what the action of the tissues is on it should also be studied.

The Object of Pharmacology.—Pharmacology may be studied as a science without reference to its application. The great interest, however, lies in its relation to the treatment of disease and to the foundations which it may lay for therapeutics. As long as we are ignorant of how a drug acts its use is empirical, unscientific and unsatisfactory. The objects of experimental pharmacology is to make every endeavor to explain the mysteries of therapeutics, and it makes little difference where this is done. In all cases, however the bedside is the court of final appeal. But clinical experience must be actual not imaginative. One of the oldest practitioners in America recently said that some physicians make the same mistake one hundred times and call it experience. Experience must be expressed in definite measured physical, chemical, physiological or psychological terms, otherwise experience is of the same value as

gossip in a court of law. Clinical and laboratory data can be expressed in these terms and are of no value if not so expressed. Mere belief that digitalis raises the blood-pressure or slows the heart is of no value unless it can be proved, and actual measurements are made. All established therapeutic agencies have at one time passed through the experimental stage, some are still in this stage.

The following work is framed with the idea that it may aid the methods of recording and the inclination to measure changes in the function of organs produced by drugs.

METHODS AND EQUIPMENT.

The success of a laboratory course in pharmacology depends to a large degree on the facilities provided. For this reason the apparatus needed should be easily available and in working order. Adequate space should be provided for keeping the apparatus. Some articles needed but rarely may be provided only when required. The greater part, however, should be in the custody of the student All apparatus that is returnable in working condition should, as far as possible, be furnished to the student.

The lockers for each group of students should contain the following:

2 semicircular stands.
5 clamps.
2 induction coils.
2 electrodes.
1 ether mask.
1 perfusion bottle.
1 Woulff bottle.
2 funnels.
2 flasks—250 c.c.
2 tumblers.
2 beakers.
2 electric keys.
2 evaporating dishes.
2 frog boards.
1 mesentery board.
1 dissecting needle.
2 25 c.c. graduates.
1 aneurysm needle.
4 Mohr clamps.
1 cork plate with pins.
1 knitting needle.
2 pithing wires.
1 brass T-tube.
1 box with 2 glass Y's, 1 glass T's and 6 vessel cannulæ.
2 camel's-hair brushes.
2 tracheal cannulæ.
1 screw clamp.
1 large screw clamp.
1 tracheal tube.
2 heart levers.

4 muscle levers—2 straight, 2 elbow.
4 watch glasses.
2 bundles of ligatures.
1 suture needle.
2 feathers.
2 10 c.c. pipettes graduated in $\frac{1}{10}$ths.
2 10 c.c. pipettes graduated in $\frac{1}{50}$ths.
1 clinical thermometer.
1 thermometer, 1° C. to 100° C.
1 blood-pressure pipette.
1 electric signal magnet.
2 glass rods.
1 syringe, 10 c.c. graduated $\frac{1}{10}$ c.c.
1 syringe, 1 c.c. graduated $\frac{1}{100}$ c.c.
4 needles in a bottle.
1 femur clamp.
2 kymographs.
2 extra drums.
1 100 c.c. cylindric graduate.
1 stomach tube and bulb.
2 gags, large and small.
2 G-clamps.
1 mercury manometer.
1 burette, stand, clamp and tube.
10 test-tubes with rack and brush.
1 sauce pan.
1 artificial-respiration bellows.
1 set of ropes.
sponge, sandpaper, wax, slides, parchment, towels, electric connection wires.
1 pair of dividers.
1 millimeter rule 10 cm. long.
2 celluloid triangles.

In addition to the equipment provided by the laboratory, each student should come provided with the following:

For operating:
1 scalpel.
2 scissors.
2 hemostatic forceps.
2 bulldog clamps.
1 operating gown.
2 towels.
2 curved needles, large and small.
2 pairs of thumb forceps—one large and one small curved.
For notes:
6 sheets of cross-section paper.
50 sheets of thin note paper.
5 sheets of carbon paper 8½ x 12 inches.

Laboratory exercises should be assigned in advance. Each student should study them thoroughly before coming to class. He should know what to expect and if the unexpected happens, he should know the reason, because results are always obtained according to the conditions under which the experiment is performed. Full records of each experiment should be kept. It is impossible for each man to keep his own record; but those of the group who are busy with the operation may be provided with a carbon copy prepared by the secretary of the group. Before commencing an

experiment, each student should have a definite part to play and should attend to this alone. Coöperation is essential to good work.

GENERAL TECHNIC.

Fluids which come in contact with the cells of the body or with living tissues should approximate as closely as possible the fluids which normally bathe these cells or tissues. Lymph and blood are the true physiological solutions. It is obviously impossible to approximate these without great care and time-consuming procedures. Several of the so-called salines are adequate for most operations and can be made with slight effort. They are isotonic, *i. e.*, they have approximately the same osmotic tension as blood. Those most in use are:

1. *Physiological Saline.*—This is merely a solution of sodium chloride in water. It should be approximately isotonic with the cell protoplasm. For mammals a 0.9 per cent. solution, and for amphibia a 0.65 per cent. solution will be found satisfactory. Although sodium chloride is quantitatively the most important saline constituent of protoplasm, the presence of several other diffusable salts is necessary to normal functioning. When cells are exposed to simple normal saline these substances soon diffuse out.

2. *Ringer's Solution.*—This more nearly approximates the normal tissue fluid and therefore prevents most of the diffusion.

For mammals:

$NaCl$	9.00 gm.
KCl	0.42 gm.
$CaCl_2$	0.24 gm.
$NaHCO_3$	0.30 gm.
Water to make	1000.00 c.c.

For amphibia:

$NaCl$	7.00 gm.
KCl	0.30 gm.
$CaCl_2$ (crystals)	0.26 gm.
Water to make	1000.00 c.c.

3. *Locke's Solution.*—

Same as Ringer's solution for mammals, to which has been added 1.00 gms. of dextrose.

4. *Tyrode's Solution.*[1]—H-ion concentration is 0.2×10^{-7}.

$NaCl$	8.00 gm.
KCl	0.20 gm.
$CaCl_2$	0.20 gm.
$MgCl_2$	0.10 gm.
$NaHCO_3$	1.00 gm.
NaH_2PO_4	0.05 gm.
Water to make	1000.00 c.c.

[1] See Rona and Neukirch, Pflüger's Arch., 1912, cxlviii, 279.

CARE OF TISSUES AND ANIMALS.

In working with tissues or with animals intelligent care is necessary to get results that are dependable. Certain things must be avoided as well as certain conditions fulfilled. In working with tissues or isolated organs, therefore, avoid:

Stretching.
Overheating.
Cooling.
Hyper- or hypotonic solutions.
Rough manipulation or handling.
Exposure to air, or drying.

The results of the above are seen especially with uterine, intestinal, or heart strips. Unless the technic and working conditions are adequate, poor and distorted results are obtained.

In working with animals avoid:

Excitement.
Hemorrhage.
Shock.
Variations in the depth of anesthesia.
Reduced temperature.
Persistent or abnormal sensory stimulation.
Too great voltage to stimulate nerves.

Use all caution to preserve the vitality of the animals, as only under such conditions can dependable and uniform results be obtained. It is highly important that the anesthesia be uniform. All drugs and those especially that act on the nervous system are greatly modified by the depth of the anesthesia, *e. g.*, digitalis produces vomiting in the normal dog, but not in the anesthetized; epinephrin will raise the pressure much more in the unanesthetized than in the anesthetized animal. Anesthesia will stop strychnin convulsions. Many other examples might be cited.

ANESTHESIA.

In most work on mammals an anesthetic is used. The choice depends upon the animal and on the experiments. Ether and chloroform are the most frequently used and unless there is an objection to it, 1 c.c. of morphin 3 per cent. hypodermically renders the procedure easier and lessens the amount of the anesthetic required. Since anesthesia is the preliminary step to other operations, it will be described first, although a demonstration of anes-

thesia is vastly superior to any written description. The mammals most used for laboratory experiments are dogs, cats, guinea-pigs and rabbits. Slightly different technic is used in the anesthetization of each.

General Principle.—The animal may be held in any convenient position, avoiding pain, excitement, injury or other distracting circumstance.

Small animals and even dogs may be enclosed in a box and the anesthetic dropped into the box through a funnel, or a wad of cotton saturated with the anesthetic may be placed in the box (Fig. 1). When the animal is sufficiently anesthetized it may be removed and the anesthetic administered by the drop method. The most

FIG. 1.—Method of anesthetizing dog in a box.

used and best laboratory anesthetic is ether. Chloroform may also be used and should be studied. A mixture of the two is sometimes used, but it is not advised. The following methods have been found convenient for the usual laboratory animals.

Dogs.—Hold the animal in the way illustrated (Fig. 2). Use a towel and fold to fit the animal's nose in the form of a cone. Drop the ether or chloroform on at a rate of about 10 drops per second and watch the reflexes. If there is no objection to it the animal may be given a small hypodermic of morphin before the ether. A small dog may be given 1 c.c. of 3 per cent. morphin sulphate and the dose repeated in fifteen minutes if thought advisable. Instead of using a towel a metal cone may be used. This may be prepared from the ordinary ether can by removing the bottom and connecting

the normal outlet with an ether bottle. The diagrams or photographs will illustrate this. The tests of good anesthesia are:

1. Loss of voluntary movements.
2. No cutaneous reflexes.
3. Slight corneal reflexes or none in deep anesthesia.
4. Even and fairly deep respiration.
5. Medium blood-pressure and pulse.

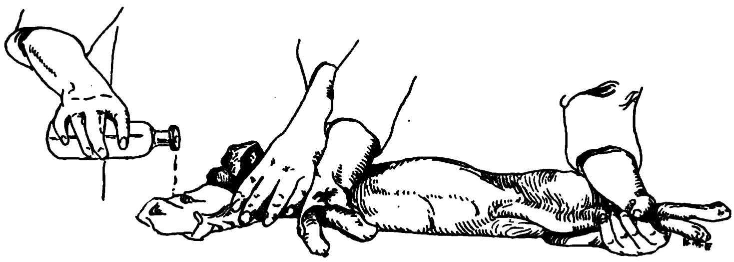


FIG. 2.—Drop method of anesthetizing a dog.

This sort of anesthesia may be continued by giving chloroform or ether from a dropping bottle at regular intervals of about thirty seconds. The number of drops that each animal requires can be determined by experiment; 3 to 6 drops every thirty seconds is recommended. It is important to maintain uniform anesthesia.

Cats.—Ether or a mixture of chloroform and ether is a good anesthesia for cats. The easiest method to use on cats is as follows: Procure a box of a size to hold the cat conveniently. Be sure that the lid fits tightly. Drop into the box with the cat a small piece of cotton saturated with ether or with a chloroform-ether mixture; 10 c.c. in broken doses will anesthetize a cat in ten minutes; glass slides in the box will permit observation. After this, proceed as with the dog. Pure ether very easily kills a cat and chloroform is more dangerous.

Rabbits.—Rabbits are best anesthetized with urethane, 2 gm. given by the mouth. Follow this with light and careful use of ether; this is given in the same method as chloroform was given to the cat. Rabbits die very readily under chloroform.

Guinea-pigs.—Guinea-pigs are anesthetized with pure ether or with ether followed by morphin, 0.1 to 0.2 c.c. of 3 per cent.

Some of the animals should be anesthetized in the box and compared with others anesthetized by the cone method. In this way the effect of the ether on the membranes of the nose, etc., can be

seen. The animals in the box show much less excitement than those which are anesthetized by the cone or towel method.

Morphin Ether.—Give a dose of 0.01 gm. per kilo (0.3 c.c. per kilo of 3 per cent.) morphin sulphate subcutaneously. After twenty minutes anesthetize the animal sufficiently with ether to permit necessary operations, such as insertion of cannulæ and sectioning of nerves. Then allow the animal to recover from the volatile anesthetic for fifteen minutes, watching closely for evidence of pain, and repeating small doses of morphin if necessary. An animal in this condition needs practically no volatile anesthetic after the operation. The objections are: (1) the morphin produces vagus stimulation and an altered heart rate, especially if there is a small amount of any toxic substance administered; (2) resuscitation is more difficult than when a volatile anesthetic is used. Three per cent. morphin is used for ease of calculation in case one wishes to convert the metric into the apothecary system. One c.c. of 3 per cent. is equal to 0.03 gm., which is equal to 0.5 grain. One c.c. of this solution is enough for a small dog.

INTRATRACHEAL INSUFFLATION.

Meltzer has devised a method of artificial respiration which is specially useful in resuscitation work and in operations where the chest is opened. Anesthesia can also be carried on by the same procedure. The method consists in driving air by means of external pressure through a tube which has been introduced through the mouth and larynx deep into the trachea. In animal work where the trachea is exposed the tube may be placed directly into the trachea. The insufflated air returns through the space between the tube and the wall of the trachea and escapes through the mouth and nose. When the size of the tube and the rate of interruption and the degree of pressure are properly selected this method will maintain life indefinitely, even in curarized animals with widely open pneumothorax.

The Tube and Its Introduction.—The tube should be flexible and elastic. It should be sufficiently large to admit the necessary amount of air and small enough to permit the return of the air between the tube and the wall of the trachea.

Introduction.—The mouth of a well-narcotized animal should be kept open by means of a gag, the tongue pulled out, and by means of a curved forceps the frenum of the epiglottis grasped and pulled back. The introduction of the tube into the larynx is then a very simple matter. Meltzer thinks that this method may also be used

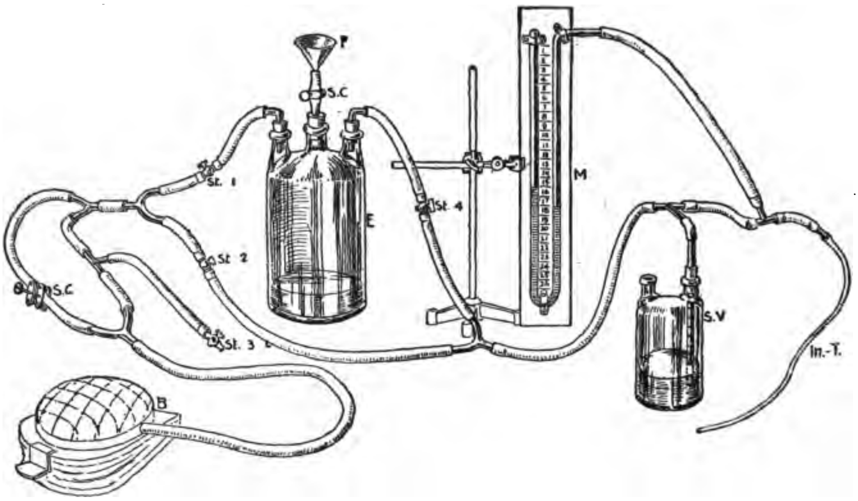


FIG. 3.—Apparatus for anesthesia by intracranial insufflation. By means of a glass blower's foot-bellows (*B*) air is driven at will through a system of branching tubes into the intratracheal tube (*In.-T.*). The first branching of the tubes is introduced for the purpose of regulating the interruption of the air-stream. From the right branch a tube is led off laterally, carrying a stop-cock (*St. 3*), which is to be used for the interruptions of the air-current. During the opening of the stop-cock a part of the air-current continues through the left tube, thus preventing too great a reduction of the pressure, which is undesirable. By means of a screw clamp (*S. C.*) the amount of air which is to pass through the left tube can be regulated; a narrowing of this tube causes a greater collapse of the lungs during the interruption. The second branching of the tubes is introduced for the purpose of regulating the anesthesia. The ether bottle (*E*) is interpolated in the left branch; the right branch runs uninterrupted outside of the bottle to unite with the part of the left tube which comes from the ether bottle. When the stop-cock in the right branch (*St. 2*) is closed, all the air passes through the ether bottle; when, instead, both stop-cocks in the left branch (*St. 1* and *St. 4*) are closed, only pure air reaches the intratracheal tube, and when all three stop-cocks are open only one-half of the air is saturated with the anesthetic. By partial closing of the stop-cocks various degrees of anesthesia can be obtained. The third opening in the ether bottle carries a tube with a funnel (*F*) through which the bottle is filled with the anesthetic; the tube is otherwise kept tightly closed by means of a screw clamp (*S. C.*). All three rubber stoppers are firmly and permanently wired down to resist various pressures. When the ether bottle is to be refilled during insufflation, both stop-cocks on the left side are closed, while the one on the right side is open. The tube which connects the anesthesia circle of tubing with the intratracheal tube (*In.-T.*) carries two lateral tubes; one is connected with a manometer (*M*), which needs no description, and the other leads to a safety-valve (*S. V.*) of a simple construction. To the rubber tubing is attached a graduated glass tube, the lower end of which is immersed under the surface of the mercury in this bottle to a depth corresponding to the pressure which is desired for the intratracheal insufflation. For instance, if the pressure should be not more than 20 mm. of mercury, the glass tube is immersed just 20 mm. below the surface of the mercury. The glass tube is kept in the desired place by means of a rubber ring resting upon the opening of the mercury bottle. This device gives great safety to the working of the method. No matter how strong and irregular the bellows is worked, the intratracheal pressure could never rise above the one arranged for; the surplus of air escapes through the tube from under the mercury. In this arrangement a wash bottle can be inserted containing warm Ringer's solution, which would serve as a filter as well as a source for heat and moisture. In our experimental work we never used it and never missed it.

in human surgery, but it has been found that the vocal cords may be injured and that spasm of the glottis tends to prevent the return of the air. After the tube enters the trachea it should be pushed gently forward until it meets with a resistance; the end of the tube is usually then in a deep place in the right bronchus. The tube should be withdrawn then 5 or 6 cm. (two or three inches). Some arrangement should now be improvised to keep it in place and to protect it from the teeth.

Insufflation Apparatus.—The figure (Fig 3) with the attached legend is self-explanatory. This is Meltzer's own description of the apparatus.

In working the bellows, interruption in the pressure should be made about eight times per minute. These need not be at absolutely regular intervals. The color of the mucous membranes will indicate the degree of oxygenation. The pressure in the manometer should be watched and not raised too high.

The tube should always be introduced with care and without force. The diameter should be too small rather than too large. There should be a safety valve to prevent the pressure rising too high. There should be at least six interruptions per minute. There should never be marked collapse of the lungs when the chest is opened, because when they collapse the walls of the vesicles tend to adhere, and it takes a dangerous pressure for distention again. It requires much less pressure to keep the lung distended.

Anesthesia by Insufflation.—Fig. 3 and the legend is self-explanatory. If too much ether has been given the insufflation with pure air is the best cure.

PHARYNGEAL INSUFFLATION.

The following method also has been developed by Dr. S. J. Meltzer, and is described in detail in the *Medical Record,* 1917, xcii, 103, and in technical paper 77 (U. S. Department of Interior, Bureau of Mines). The method was developed because of some disadvantages in the method of intratracheal insufflation by the same author. These drawbacks are as follows: (1) The introduction of a tube into the trachea requires some dexterity and practice, and (2) the apparatus available on the market used for keeping up intratracheal insufflation is expensive. It is therefore improbable that the apparatus and the experienced operator will be at hand in many cases when needed. The method of intrapharyngeal insufflation is simple and efficient. The apparatus is seen ready for use in Fig.

4. Instead of the bellows, as seen in the picture, an oxygen tank may be used. Following is the manufacturers' description and explanation of the apparatus, which is not patented and rather inexpensive.

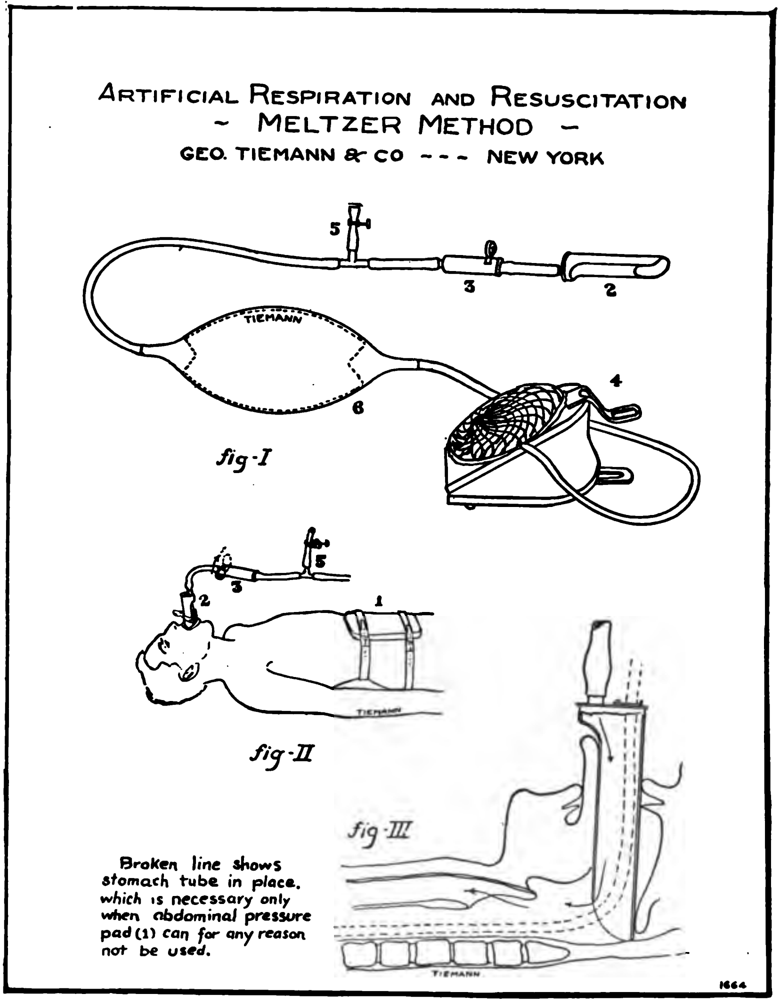


FIG. 4

Artificial Respiration and Resuscitation by the Meltzer Method.—The Meltzer method of artificial respiration is based upon the principle of *pharyngeal insufflation*, a process that consists in expanding the lungs with air at regular intervals of about twelve to the minute

and *depending on the elasticity of the chest walls to expel* a portion of the air during each intervening period. In using the apparatus a board is first strapped tightly over the abdomen, Fig. 4 (*II, 1*), to prevent the stomach instead of the lungs from being expanded with the air.

The pharyngeal tube attached to the apparatus is then placed in the mouth and pushed as far back as it will go, Fig. 4 (*III*), and the tongue is drawn forward and tied to the tube, Fig. 4 (*II, 2*). The tube pushes the soft palate upward and effectually closes the passageway through the nose, Fig. 4 (*III*) so that no air can escape through the nostrils, while an opening in the bottom of the tube permits the air to pass freely down the throat.

For supplying the air, a foot bellows is used, Fig. 4 (*I, 4*). As the air is conducted through the tube it passes a valve (3) which regulates the inspiration and expiration. With watch in hand, or in synchronism with his own respiration, the attendant turns the ring that governs this valve alternately to the right and left at regular intervals.

When the ring is turned to the right the air is forced into the lungs, and when the ring is turned to the left the air is shut off, at the same time a small vent is opened and the air escapes from the lungs. Just below this valve is another valve for regulating the pressure of the air given the patient, Fig. 4 (*I, II, 5*).

At the start the pressure used is very low, but is increased by gradual closing of the valve, until the chest shows a regular normal heaving.

In case the apparatus is hurriedly called into use during an abdominal operation, in which case the abdominal board (1) cannot be strapped on, a stomach tube is passed through the pharyngeal tube, through the esophagus and into the stomach, Fig. 4 (*III*).

An important feature of the apparatus is that it can be operated by one man, who need not be an expert. The bellows is worked by the foot and the respiratory valve is operated by the right hand, leaving the left hand free for making any adjustments that may be necessary.

Parts Composing Meltzer's Device for Artificial Respiration by Pharyngeal Insufflation.—1. Abdominal pressure pad.

2. Pharyngeal tube.

3. Respiratory valve.

4. Foot bellows.

5. T-tube with a screw clamp, interpolated between the respiratory valve and the foot bellows. Pharyngeal tube, respiratory

valve, T-tube and foot bellows should be kept connected by means of good rubber tubing which does not kink. The apparatus will then be in readiness for immediate application.

6. Air bag to give uniform flow of air.

7. Tongue forceps and tape (or gauze bandage) for tying the tongue to the pharyngeal tube.

8. Stomach tube fitting into the opening of the pharyngeal tube to be used for the escape of surplus air from the stomach in cases where no pressure can be exerted upon the abdomen.

Order of Procedure.—1. The pressure pad is applied to the abdomen.

2. Tongue drawn out.

3. Pharyngeal tube is inserted into the mouth until it reaches the posterior wall of the pharynx and then the drawn out tongue is tied to the pharyngeal tube. This will keep the epiglottis raised and the tube in its proper place.

4. An assistant operates the bellows while he takes the respiratory valve in his hand and moves the ring from side to side by the thumb, synchronically with his own respirations.

5. The screw clamp on the T-tube is immediately screwed down until the chest shows a proper heaving.

The heaving of the chest need not be too strong. A satisfactory number of respirations should be established twelve to fifteen per minute. If the air tends to accumulate in the stomach, or in cases in which the abdomen is open and the board cannot be applied a stomach tube is inserted. The air escapes through and around the tube. Details of the procedure and its application to clinical problems are given clearly in the references.

The Schäfer Method of Artificial Respiration and Resuscitation.—This method was devised by Dr. E. A. Schäfer, Professor of Physiology in the University of Edinburgh. He recommends that the patient be placed in a prone position with the head slightly lower than the body. The physician or operator is astride or to the side of the patient, and the open hands are placed on the patient's side at the level of the lower ribs, and firm but not too violent pressure is applied. This is done by allowing the weight of the operator to come on the arms. After this pressure has been applied for about three seconds (Fig. 5, *a*) the pressure is relaxed by raising the body (Fig. 5, *b*). The pressure and relaxation should be made about twelve times a minute; the amount of air entering the lungs under these conditions is as much as or more than in ordinary respiration.

He found that in a normal person the amount of air exchanged

in a minute is about 585 c.c. when the respirations are thirteen times a minute, or an average of 450 c.c. of tidal air at each breath. With his method of artificial respiration he was able to pump 6760 c.c. through the lungs in a minute; when compared with other methods of respiration he found this method the most efficient.

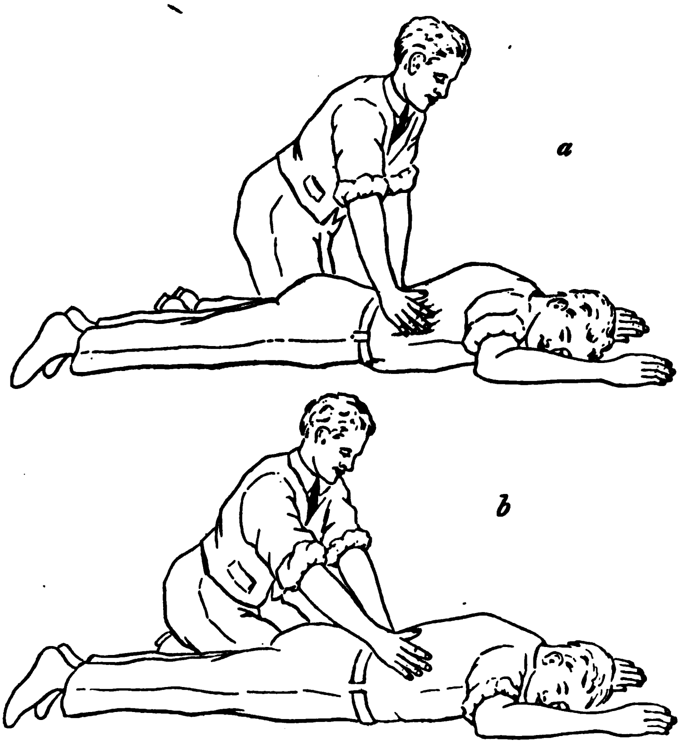


Fig. 5.—Schäfer's prone-pressure method of artificial respiration. *a*, pressure being applied; *b*, pressure removed.

The advantages of the method are:

1. It is fully efficient.
2. It can be performed without fatigue by a single individual.
3. It is simple and easily learned.
4. It allows the tongue to fall forward and the mucus and water to escape from the mouth, so that the tendency of these to block the passage of air which is inherent to the supine position is altogether obviated.

Other methods of artificial respiration may be mentioned, but they are of historical interest only: They are:

The Marshall Hall Method.—The Marshall Hall method consists of rolling the patient alternately from the prone position to the lateral position and pressing between the shoulder-blades when he is in the prone position. Schäfer found that by this method the tidal air volume was 254 c.c. as against 520 c.c. for his own method, or 3300 c.c. per minute as against 6760 c.c.

The Sylvester Method.—In this method the patient lies on his back, with the shoulders raised and the head hanging low. The operator takes hold of the patient's arms above the elbow and raises them away from the body until they arrive at about above the patient's head. This raises the ribs and increases the capacity of the chest. The arms are then lowered by his side and the elbows flexed and pressed against the lower part of the chest. This diminishes the air-holding capacity of the chest by driving the air out. The tongue is likely to fall back into the throat and impede respiration unless someone grasps it and pulls it forward.

The tidal air by this method Schäfer found to be only 175 c.c. and the air exchanged a minute only 2280 c.c. as against 520 c.c. and 6760 c.c. respectively for his own method. Other methods were investigated by Schäfer and by the recent National Committee, who corroborated Schäfer's findings.

The Third Resuscitation Commission.

The subject of resuscitation is so important that we cannot do better than include a report of the Third Resuscitation Commission, which explains itself, and which shows the importance of the subject in Medicine.

To save space we have eliminated some non-essential matter from the report which is complete in *Science,* December 6, 1918, p. 563.

The commission included leading investigators in physiology, pharmacology, medicine, surgery and engineering, administrative officers of Army, Navy and Public Health Services, and finally representatives from the larger electrical companies where the problems of resuscitation have to be dealt with daily. As originally constituted it consisted of fifteen men. Later four others were added in an advisory capacity.[1]

[1] There were present at the meeting: Past Assistant Surgeon E. F. Du Bois, U.S.N.R.F., of the Bureau of Medicine and Surgery, Navy Department; Dr. D. L. Edsall, Professor of Medicine and Dean of Harvard Medical School; Mr. W. C. L. Eglin, Chairman of Committee on Safety Rules and Accident Prevention of the National Electric Light Association; Dr. Yandell Henderson, Professor of Physiol-

The practical difficulties in life-saving problems are these:

A mechanical life-saving device is not immediately available, the possession of such an apparatus gives a false sense of security, so that life-guards, policemen, medical students and even hospital physicians are not adequately trained in either handling the apparatus or the manual methods.

In view of these facts the committee advised that the prone-pressure method of Schäfer is preferable to any other manual method. Instruction in this method should be included in the training of all people likely to handle this class of cases. When such an emergency arises the manual method is to be applied at once and continued during the transportation of the individual to hospitals or first-aid stations. Efforts on resuscitation should be continued until spontaneous breathing is permanently established. This means that patients must be watched for a definite period after respiration is established. In the absence of all signs of life the method is not to be abandoned until after an hour's trial. It is not to be used in cases of coma where normal respiration continues. In cases of gas asphyxia the simultaneous administration of oxygen is advised.

During all stages of resuscitation the body heat is to be maintained.

Mechanical devices should be confined to hospitals and institutions. They should be investigated further with a view to their perfection.

Fourteen members agreed to the above report. Henderson took the stand that really efficient and reliable devices existed already,

ogy, Yale University, and Consulting Physiologist of the Bureau of Mines; Dr. William H. Howell, Professor of Physiology and Assistant Director of the School of Hygiene and Public Health, Johns Hopkins University, Member of the National Academy of Sciences; Dr. Reid Hunt, Professor of Pharmacology, Harvard Medical School and Secretary of the Commission; Prof. A. E. Kennelly, Professor of Electrical Engineering at Harvard University and the Massachusetts Institute of Technology; Dr. Charles A. Lauffer, Medical Director of the Westinghouse Electric Company, Pittsburgh, Pa.; Dr. S. J. Meltzer, Rockefeller Institute, Chairman of the Commission and Member of the National Academy of Sciences; Dr. Joseph Schereschewsky, Assistant Surgeon-General, U. S. Public Health Service; Dr. G. N. Stewart, Professor of Experimental Medicine, Western Reserve University, Cleveland; Prof. Elihu Thomson, General Electric Company, West Lynn, Mass., Member of the National Academy of Sciences; Lieut-Col. Edward B. Vedder, of the Army Medical School; Major Frank G. Young, of the Ordnance Division of the War Department.

A telegram was received from Surgeon-General Gorgas that Dr. Charles H. Frazier, Professor of Surgery, University of Pennsylvania, is to represent his office. (In a subsequent communication, Major Frazier accepted his appointment.) Conferees: Mr. P. H. Bartlett, Philadelphia Electric Company; Mr. Wills Maclachlan, Electrical Employers' Association, Toronto, Canada; Mr. C. B. Scott, Chairman of the Subcommittee on Accident Prevention National Electric Light Association; Dr. F. E. Schubmehl, General Electric Company, West Lynn, Mass.

but that their results were inferior to manual methods and that they actually contribute to decrease in life saving, because of the false assurance they give. He felt that they should all be abandoned in favor of the manual prone-pressure method.

Resolutions Adopted by the Commission.

In the discussion following the presentation of methods and evidence to the commission the following important facts were emphasized:

1. That in most accident cases no resuscitation apparatus is at hand for immediate use.

2. That reliance upon the use of special apparatus diminishes greatly the tendency to train persons in the manual methods and discourages the prompt and persevering use of such methods.

3. That police officers or physicians often interfere with the proper execution of manual methods, in that they direct that the patient be removed in an ambulance to some hospital, thus interrupting the continuance of artificial respiration.

4. That in many hospitals the members of the staff are not all acquainted with the methods of artificial respiration.

5. That in medical schools instruction is not properly provided for students in the manual methods of artificial respiration.

In view of these facts the following resolutions were adopted by the commission:

1. The prone-pressure, or Schäfer, method of resuscitation is preferable to any of the other manual methods.

2. Medical schools, hospitals, fire and police departments, the Army and Navy, first-aid associations and industrial establishments in general should be urged to give instruction in the use of the prone-pressure method of resuscitation.

3. Individuals who, from accident or any other cause, are in need of artificial respiration should be given manual treatment by the prone-pressure method immediately on the spot where they are found. It is all-important that this aid be rendered at once. The delay incident to removal to a hospital or elsewhere may be fatal, and is justifiable only when there is no one at hand competent to give artificial respiration. If complications exist or arise, which require hospital treatment, artificial respiration should be maintained in transit, and after arrival at the hospital, until spontaneous respirations begin.

4. Persons receiving artificial respiration should, as much as possible, be kept warm and the artificial respiration should be

maintained until spontaneous breathing has been permanently restored, or as long as signs of life are present. Even in cases in which there is no sign of returning animation, artificial respiration should be kept up for an hour or more.

5. A brief return of spontaneous respiration is not a certain indication for terminating the treatment. Not infrequently the patient after a temporary recovery of respiration stops breathing again. The patient must be watched, and if normal breathing stops, the artificial respiration should be resumed at once.

6. Artificial respiration is required only when natural respiration has ceased. In cases of simple unconsciousness from any cause in which natural respiration continues, artificial respiration should not be employed without medical advice.

7. The commission recommends that in cases of gas asphyxiation, artificial respiration, whether given by a manual method or by special apparatus, should be combined, when possible, with the inhalation of oxygen from properly constructed apparatus.

8. With regard to the employment of mechanical devices for artificial respiration the commission feels that it ought not at present to take a definite stand either for or against any particular form of apparatus. However, the commission recommends, that the use and installation of apparatus should be confined, for the present, to properly equipped institutions under medical direction. The commission recognizes the great need of simple devices capable of performing artificial respiration reliably and efficiently. It therefore recommends a careful study of the problem, directed toward *the development of a reliable method appropriate for general adoption*. Such studies can best be carried on in properly equipped hospitals and laboratories which offer opportunities and facilities for critical observation and experimentation.

In view of the importance which the knowledge of proper methods of resuscitation possesses for public health and safety, and considering the fact that many practitioners, members of hospital staffs and graduates of medicine are not thoroughly familiar with the methods of resuscitation, especially that of the prone-pressure method, the commission recommends:

(*a*) That medical journals (and other scientific and practical journals which are interested in the problem of resuscitation) be asked to publish the resolutions adopted by the commission.

(*b*) That a copy of these resolutions be sent to the medical colleges with a request that proper instruction in this subject shall be arranged for in the *college schedules*.

(*c*) That these resolutions be sent to as many hospitals as possible, with the recommendation that members of the house staff shall familiarize themselves with the methods of resuscitation.

(*d*) In order that the resolutions of the commission may be brought to the attention of interested circles (fire and police departments, industrial plants, etc.) it was agreed that they be communicated to the Associated Press (by the National Electric Light Association).

CHAPTER I.

MODES OF ADMINISTERING DRUGS.

Frogs.—Drugs are usually injected into the anterior or posterior lymph sac. Since these beat rhythmically a quick entrance into the circulation is assured. The best method is to introduce a hypodermic needle through the floor of the mouth and down into the anterior lymph sac. Direct injection into the lymph sac may be followed by a leakage through the needle hole, consequently it is a less accurate method. By going through the mouth there is little likelihood of this error. Demonstrations of each method should be given. See Fig. 25, p. 112.

Mammals.—The methods used are: (1) By mouth; (2) subcutaneously; (3) intramuscularly; (4) intravenously; (5) intraperitoneally; (6) by rectum; (7) intraspinally or subdurally.

1. *By Mouth.*—When the volume is small the drugs may be given conveniently in a capsule. The animal's mouth is held open, the head back and the capsule thrown back or placed far back on the tongue. Hold the animal's mouth shut, and if he does not swallow it spontaneously slap the throat gently or rub it toward the stomach. There is usually no trouble to get the animal to swallow. Fig. 31, p. 134.

The liquids are most conveniently given by stomach tube. Hold the animal firmly; open his mouth and insert an appropriate wooden gag, with a hole in it, behind the molar teeth. Introduce a gum-elastic catheter through the hole of the gag and push it into the stomach. Pour the liquid through the tube by means of a funnel. It is unnecessary to state that the tube may, in some cases, enter the lungs instead of the stomach. This may be ascertained by listening for respiration. If the tube is in the trachea, respiration is heard through it. In such cases, withdraw and reinsert. By pulling the tongue forward one may see the tube in the proper location (Figs. 6 and 7). A demonstration of the serious consequences of putting fluid in the lungs is valuable.

2. *Hypodermic Injection.*—Hold the skin between the fingers and with a quick, firm thrust insert the needle. Since the dog's skin is thick and the animal will move, if not held carefully, care must be taken not to break the needle.

FIG. 6.—Method of introducing liquid into the stomach of a rabbit.

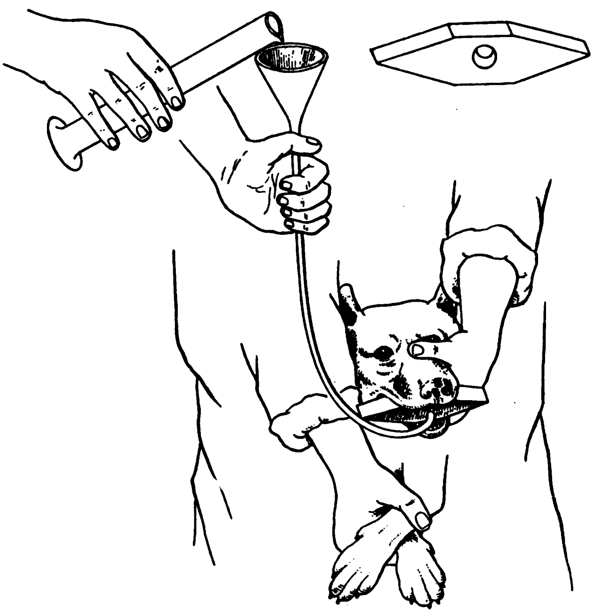


FIG. 7.—Method of introducing liquid into the stomach of a dog.

3. *Intramuscular Injections.*—This may be made into any large muscle; a quick thrust into the middle of the muscle is best.

4. *Intraperitoneal Injection.*—This is an excellent method when large volumes are to be injected. Grasp a fold of the skin and muscle of the flank or along the linea alba and inject perpendicularly.

5. *Intravenous Injections.*—(*a*) This may be done in unanesthetized animals by pressing the leg or jugular regions until the veins stand out; then the needle can be readily introduced.

(*b*) When large volumes are to be introduced it may be well to insert a cannula in the vein and attach a burette, with saline solution, by means of a rubber tube. Injections may then be made into the tube and washed in from the burette.

FIG. 8.—Method of introducing needle into the fourth ventricle.

(*c*) In case of rabbits the ear vein is used. The injection may be facilitated by shaving the ear and rubbing it with toluol or some irritating drug. A clip attached centrally will make the peripheral bloodvessels stand out so that injection may easily be made.

6. *Intraspinally, Subdurally, or into the Fourth Ventricle.*—To inject the fourth ventricle, this at first should be done on an anesthetized animal. After the technic has been obtained it is easily carried out without an anesthetic, and causes but slight pain. Flex the head of the animal strongly on its chest. Insert a thin needle between the occiput and axis. Point toward the nose of the animal in the flexed position. When the needle has entered the ventricle, a clear fluid escapes freely (Fig. 8).

Injections into the subdural spinal region are made by passing the needle along the side groove of the vertebra, keeping in the straight line as much as possible. Done this way, an entrance between the vertebra can be made. This should first be shown on the skeleton.

7. *Rectal Injections.*—These are made through a catheter. When the desired amount of fluid is introduced a clamp or forceps may be applied to keep it from being expelled. If the drug is irritating it should be mixed with gum acacia, 6 per cent., or some other colloidal material. This will lessen the irritation.

OPERATIVE TECHNIC.

Students in pharmacology have already had a course in physiology, so that it is unnecessary to detail operative technic. If this is done it is so voluminous that it detracts from the object of the experiment. If such a course is needed a few minutes of demonstration is worth hours of reading. For these reasons principles only are given.

Exposure of Nerves.—Determine the approximate position of the nerve to be exposed. Make the superficial incision about three times as long as the nerve is below the surface. Work mainly by blunt dissection, but avoid hemorrhage by ligating or clamping bleeding vessels. Do not let the nerve become dry. Keep it moist with a saline or with the body fluids. Keep it covered with the tissues as much as possible. If necessary to pass a ligature to raise it for stimulation, use linen or gauze strips. For very small nerves, silk threads are better.

Stimulation of Nerves.—This is done most conveniently in experimental work by means of electrodes; salts, etc., may also stimulate. Never stretch or pinch a nerve. Do not let it become dry, but keep it moist with physiological saline. Do not use a current strong enough to burn the nerve. No current should be used on a nerve that is decidedly unpleasant when held to the tongue.

Placing a Cannula in the Trachea.—The animal is placed in position on the operating table and tied securely, with head extended and throat exposed. Make a deep median incision at one cut, through the skin, muscles, etc., down to the trachea with the face of the knife. Do not pick at it, but cut with decided intent. When such a cut is made, place the index fingers in it and pull the fascia apart. In this way the trachea, nerves and vessels may be exposed clearly and without bleeding. In some instances where a goitre

lies in the field of operation, special precautions must be taken to stop hemorrhage. The objects of placing a cannula in the trachea are:

1. To render easier the process of anesthesia.
2. To permit artificial respiration.
3. To facilitate resuscitation in cases of accident.

Fig. 9.—The most important anatomical structures in the dog's neck. *1*, cannula in the trachea; *2*, three-way cannula in the carotid artery; *3*, trachea; *4*, *5*, vagosympathetic nerve; *6*, thyroid gland; *7*, rubber tube from the cannula to the pressure bottle; *8*, rubber tube leading to the mercury manometer.

A tracheal cannula is never inserted in animals which are to be kept after the operation.

To place cannulæ in veins, arteries, ducts, etc., little need be said. A knowledge of the anatomy of the region is important and must be gained by dissection and practice, and this is one of the beneficial results of a laboratory course. The object of such cannu-

lation is the obtaining of records of blood flow, salivary secretion and the like. Cannulæ are placed in veins for the injection of fluids. This cannot always be easily accomplished by means of hypodermic, because in cases of collapse the veins of small animals are in many cases invisible. When a cannula is inserted, and this may be attached to a burette with a rubber tube, injections can be made into the rubber tube, and the pressure from the burette will carry it into the vein even when the heart is feeble or stopped.

Injecting into a Vein.—Fill a burette with salt solution (all solutions injected should be about 40° C.) Attach a rubber tube, with pinch-cock or screw clamp, to the lower end of it, if there is not a glass stop-cock on it. The burette should then be filled with 0.9 per cent. NaCl solution, as also the tube. Make a longitudinal incision about two inches long on the skin over the anterior surfaces of the thigh, near the middle of Poupart's ligament, to expose the femoral vein; the artery can be felt through the intact skin. Blunt dissection with the handle of the knife in Scarpa's triangle will expose the vein; place two ligatures about it as in placing the carotid cannula. Then pick out a cannula of the proper size, allowing for more shrinkage of the vein than of the artery. The distal ligature should then be tied, the vein cut, the cannula introduced and tied in place. Then fill it with 0.9 per cent. NaCl and connect with the rubber tube on the burette. (If any considerable volume is to be injected it should be at body temperature.) Be sure that all air bubbles have been carried out by the liquid. Drugs can be injected by a syringe through the walls of the rubber tube obliquely and the solution carried into the vein by letting in a little salt solution.

Inserting a Cannula into the Carotid Artery.—Find the artery in the trough outside and behind the muscles covering the trachea. The vagus nerve, which is in the same sheath, appears white; the internal jugular vein is bluish purple and the artery, light bluish or pink. Separate it entirely from the surrounding structures by blunt dissection for about an inch and a half; be careful not to injure the vagus nerve. Put two ligatures around the artery, one below and one above where the cannula is to be inserted. The upper one is to be tied tightly. Select a cannula whose diameter is almost equal to that of the artery. Put a pair of bulldog forceps on the artery just below the cannula. Make a small incision about half-way through the diameter of the artery into the lumen of the artery. Take hold of the lower end of the incision with a pair of fine forceps and insert the cannula with the projecting end of the beveled tip

toward the forceps. Put the cannula into place and fasten it with the ligature.

Opening the Thoracic Cavity.—The thoracic cavity is opened to study the heart and lungs. To do this the breastplate is removed to such a degree that observations and manipulations may be made. The main points to watch in this operation is not to injure the lungs, and to tie the large vessels either before they are severed or to ligate them quickly if they are bleeding. The whole technic has these objects in mind. Otherwise the method of work has little meaning. Insert a tracheal cannula and see that the ether bottle and accompanying apparatus are all ready for immediate use before work is started. Have a number of hemostats ready. Dissect along the midline of the neck down to the manubrium sterni, using blunt dissection as much as possible. On each side of the midline, make an incision through the skin; also one an inch from the midline for the entire length of the sternum. Use blunt dissection and expose the first rib on each side and begin artificial respiration. In the first right interspace insert an aneurysm needle and turn the handle so that the hook is upward and embraces the first rib. Pull it up. Then cut it through with bone forceps and enlarge the opening. Be sure that the lung is expanding so that the tip is close to, but is not protruding from the opening in the chest wall. Be sure also there is good lung ventilation. Just exposed by the opening, at the margin of the anterior mediastinum, will be found the right internal mammary artery; place a clamp about it. Expose and clamp the left internal mammary artery also. With scissors, cut through the muscles covering the right side of the chest and through all the right ribs with bone forceps and scissors, using hemostats on all the bleeding parts. If the index finger is inserted into the thoracic cavity and used as a guide, cutting into the lung may be avoided. The sternum may be cut through with bone forceps. Hemostats will be required to clamp bleeding-points, which are always found at the site of the internal epigastric vessels near the lower end of the sternum.

The chest is more easily opened and the contents exposed with less bleeding by a midline incision; but in this case there is little room for work within the chest since it is hard to hold the walls back and give room for such instruments as the myocardiograph. Some workers, however, prefer the midline incision, and if the attempt is made to preserve the animal after such an operation, this is the only method applicable.

RECORDING BLOOD-PRESSURE IN MAMMALS.

No one method of recording blood-pressure is satisfactory to all experimenters. The technic varies with the facilities of the laboratory. If the student has become familiar with any of the usual methods he will find it adequate. All methods depend upon the same principle, namely, the insertion of a cannula in an artery and the transmission of the arterial pressure to a recording instrument or manometer.

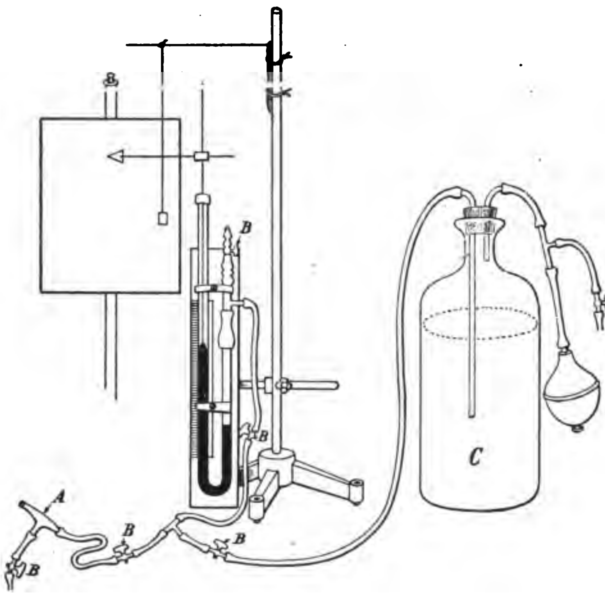


FIG. 10.—Apparatus for direct measurement of blood-pressure. *A*, 3-way cannula for insertion into artery; *B*, valves to regulate pressure; *C*, pressure bottle.

To measure the pressure etherize the animal in the usual way and insert a tracheal cannula. The tracheal cannula is convenient though not absolutely necessary. It gives a more perfect control of the animal and artificial respiration can be given at any time, should it be needed. Insert the three-way cannula into the central or cardiac end of the carotid artery. The cannula should have a piece of rubber tubing on each of the other ends. After the cannula is tied into the artery connect one end of it by means of a rubber tube with the manometer. See that it is now filled with the anticoagulant solution, either sodium citrate, 5 to 10 per cent.; magnesium sulphate, 6 per cent. or other solution as may be provided.

See that the system is well filled and contains no air. The other free end of the three-way cannula is connected in the same way with a pressure bottle.

The pressure bottle may be used as in the illustration where the pressure is transmitted by a hand pump to the anticoagulant fluid, or if the air system of raising the pressure is not used, the pressure may be raised by a pressure bottle suspended at a height of approximately six to eight feet above the operating table. If the pressure bottle is used it must be made safe as it has been known to fall and injure the operator. This last method is used in many cases where a permanent working place is provided. Either method is satisfactory.

Clotting is lessened in the three-way cannula by having a bulbous enlargement and the use of an anticoagulant solution. The enlargement of the three-way cannula permits mixing of the blood with the anticoagulant solution.

The pressure in all cases should be raised to nearly that of the blood-pressure of the animal before the clip is released from the artery, because if the blood flows out into the connecting tubes it may clot and thus cause considerable annoyance and inconvenience, and it also takes the blood from the vessels of the animal and lowers the normal blood-pressure to that extent. If it can be made to balance within the three-way cannula this is much more satisfactory from all standpoints. If too great a pressure be placed on the outside, some of the anticoagulant is forced into the heart with fatal effect in most cases.

Cleaning Out the Cannula.—Place a bulldog clamp on the artery again, and place a pinch-cock on the tube connecting with the manometer. Slip the tube off of the cannula and swab the cannula with a feather. Fill the cannula system with $MgSO_4$ solution (6 per cent.), sodium citrate 5 per cent., or any other anticoagulant solution. The main points to observe in washing out the cannula is that fluid be not injected into the heart, or clots or air washed into the circulation. If the cannula is to be cleaned after it is removed from the body, it may be soaked in 5 per cent. NaOH for some time. This dissolves the blood, fibrin, etc.

RECORDING RESPIRATION.

Insert a tracheal cannula and connect it with one horizontal limb of a T-tube by means of a short rubber tube. The other horizontal limb of the cannula is connected with the ether bottle. The

vertical limb of the T-tube is connected with a rubber tube long enough to reach a tambour registering on a kymograph drum. (Records of respiration obtained in this manner are comparable only so long as the openings into and from the ether bottle are kept constant. It is evident that if these are adjusted during the course of the experiment, there is bound to be an inaccuracy in the record.

GRAPHIC RECORDS.

In making these records, the writing levers, tambour, etc., must be so arranged that all writing points are in the same vertical line. In most cases it is a good idea to have a time record. If the laboratory has a "time" circuit, this is connected with a signal magnet writing on the drum. If such a circuit is not available, the time magnet is connected in series with a dry cell and key. A student should be prepared, with a watch before him, to make contacts at stated times. Accuracy in this matter is assured by close attention only. The wire connection should be long enough so that the operator will not be in the way of the experimenting. Individual metronomes are often used to make and break the time circuit; the time magnet may be adjusted in blood-pressure experiments to register the zero pressure. A second signal magnet is arranged to write directly under the first to record the instant and duration of the given procedure. The key controlling this magnet should be on the drum table conveniently near to the operator.

When the record is completed, it should be taken from the drum and labeled at once to prevent confusions which might arise. The date and series, if more than one record is made on one day, should be *written on the record.* It is advisable to put all data possible on the tracing. Each experimental procedure should be legibly specified. The time of each event should be specified on the record in order that calculation may be made later of the duration of the experiment and the intervals between events. A writing board or a large glass plate facilitates the labeling of the records. It should have a base large enough to hold the record and a ledge with a hand rest at each side. After the records are labelled, they should be shellacked. When a series of records is made and properly labelled, they afford data on the experiment to be studied at leisure. The important sections may be copied as blue prints and given to members of the class.

Records of blood-pressure may be studied as follows: Careful measurement of the distance of the tracings above the base line at

various points along the course of the curve should be made. This means, before the drug is injected, after it is injected, and when the action becomes apparent, and at intervals thereafter according to the drug used. When the curve is ordinarily uniform, readings every minute are often enough. The zero line marked on the tracing is always used to determine the blood-pressure. The distance above the base line should be doubled, as there are two arms of mercury in the manometer. The changes in the heart-rate are studied as follows:

Two parallel lines are drawn perpendicular to the base line so as to intersect the tracings. The distance of the lines from each other is determined by the rate of the drum as indicated by the time marker. They are usually drawn to include between them a space of ten seconds, in terms of the record. The number of heart beats on the tracing included between the two lines is counted and the rate of the heart per minute is calculated from this; these estimates are made along the curves at the same places where the pressure changes are measured. Mark any other variation in the curve, as irregularities of heart action or of respiration.

CHAPTER II.

EXPERIMENTAL PHARMACOLOGY.

Substances Whose Main Action is Local. This will include mainly the pharmacology of:

I. The skin.

II. The visible mucous membranes of the:

- Eye.
- Mouth.
- Nose.
- Throat.
- Rectum.
- Vagina.
- Urethra.

III. The alimentary tract.

In presenting pharmacology in the laboratory, the logical sequence that is followed in a lecture course, may be very inconvenient. For this reason sequence is frequently sacrificed to convenience without detracting greatly from the value of the work.

I. *The Skin.*—The functions of the skin are varied and complex. The most important are:

1. It is the protective covering of the body.
2. It is the sensory surface which adjusts the body with the outer world.
3. It regulates the body temperature, or at least is one of the adjusting mechanisms.
4. It is an excretory organ.
5. In some cases it is a secretory organ, (milk for example).

Many of these functions will fall better under the heading of Glands, Peripheral Nerves, Intestines, etc. For that reason in the Pharmacology of the Skin we will study (1) those drugs that act locally mainly because of their mechanical effect; (2) those that have an action on the skin due to the excretion of drugs by the skin.

Classification in pharmacology is for convenience only and as an aid to the association of drug action. It cannot be anything but arbitrary and overlapping. Drugs used mainly for their action on the skin are:

1. Dusting powders.
2. Emollients and demulcents.
3. Collodions.
4. Irritants and counterirritants.
   - Rubefacients.
   - Vesicants.
   - Pustulants.
5. Antiseptics and disinfectants.
6. Corrosives and caustics.
7. Local anesthetics.

Drugs that act on the skin either through excretion by the skin or through metabolic changes and includes especially:

- Iodides.
- Bromides.
- Salicylates.
- Quinin.
- Arsenic.
- Chloral.
- Antypyretics.
- Sulphonal.
- Aspirin.

8. Poultices.

II. Drugs used for their action on the visible mucous membranes:

1. Demulcents and emollients.
2. Bitters.
3. Astringents.
4. Corrosives and caustics.
5. Antiseptics.
6. Local anesthetics.

These may be used in the form of gargles, lozenges, suppositories, nebulæ, injections, etc.

III. Drugs used mainly for their action on the alimentary tract are:—

1. Demulcents and emollients.
2. Astringents.
3. Antiseptics and disinfectants.
4. Carminatives.
5. Bitters.
6. Digestants.
7. Emetics.
8. Anti-emetics.
9. Acids and antacids.

10. Absorbents.
11. Drugs to lessen movement (opiates, etc.)
12. Drugs to increase movements (cathartics.)
13. Anthelmintics.

LOCAL ACTION OF DRUGS.

Local Anesthesia (an, not; aisthetos, sensible).—Local anesthesia, or terminal anesthesia, may be brought about by suppressing the sensitivity of the nerve ends—terminal anesthesia, or by blocking the nerve impulse in the nerve trunks—nerve blocking.

Methods.—Local anesthesia may be brought about by:

1. Compression.
2. Cold applications.
3. Chemical agents.
4. Local anemia.
5. Infiltration with anisotonic solutions—water, salt solutions, etc.—which act purely physically.
6. Cocain and substitutes, which may be considered as a special class of chemical agents.

The chief local anesthetics are:

Ethyl chloride.
Ether spray.
Extreme cold.
Cocain and substitutes—prococain and tropococain.
Chloretone.
Antipyrin.
Hydrocyanic acid.
Creosote, guaiacol.
Iodoform.
Orthoform.
Phenol.
Quinin urea hydrochloride.

Local Anodynes:

Aconite.
Veratrin.
Belladonna.
Menthol.
Chloral.
Sodium bicarbonate.
Zinc oxide.
Volatile oils.

Experiment I.—Cutaneous Sensations.—General Characteristics.—(*a*) *Punctiform Distribution of Cutaneous Senses.*—Shave and mark off an area of skin on the back of the hand about one inch square. Blindfold the subject and arrange the hand on a comfortable support. With suitable esthesiometers explore the selected area systematically for warm, cold and pressure spots, marking each variety in a different color, say red, blue and black respectively. It will require close attention to recognize the sensation aroused in a touch spot and to distinguish it from that of a pain spot, the sensation lasting longer in the second case. Observe the arrangement and relative numbers of the several kinds of sensory spots. Note the variation in sensitiveness within each group and select for later experiments a few of the more sensitive cold and warm spots.

(*b*) *Specific Nerve Energies (Functions) of the Cutaneous Nerves.*—Try mechanical or electrical stimulation of a cold spot. Try the paradoxical cold reaction, *i. e.*, stimulation of a cold spot by application of a warm object with a temperature of 50° to 60° C.

(*c*) Spray the area with ethyl chloride and repeat (*a*) and (*b*).

(*d*) Compress the arm to a degree when the circulation is markedly disturbed and repeat (*a*) and (*b*).

Experiment II.—Temperature Sensations.—(*a*) *Adequate Temperature of a Medium.*—This is the temperature of the medium which gives neither warm nor cold sensation. It is not a definite temperature, but a temperature range, the extent of which depends on certain physical properties of the medium, such as its specific heat, its conductivity—for heat, the character of its surface, etc. Compare oil and mercury, water and mucilage of acacia, at the same temperature. Practical method of finding the temperature of the skin.

(*b*) *Adaptation.*—Transfer the finger from a bath of Hg. at the adequate temperature to Hg. a few degrees colder; the initial sensation soon disappears. Repeat this with colloidal solutions at the same temperature.

(*c*) *Contrast.*—Find the adequate temperature of water for the fingers of both hands (approximately 28° C.). Then transfer the right hand finger to water at 15° C., the left hand finger to water at 40° C. After a short interval return both to the water at the adequate temperature—about 28° C. What sensations result?

Experiment III.—Pressure Sensations.—(*a*) Observe the arrangement of the spots in relation to hair follicles and demonstrate the influence of the fine hairs magnifying the effect of weak stimuli.

(*b*) *Absolute Threshold—Liminal Stimulus.*—This depends on a number of factors, such as the quality of the skin, presence or

absence of short hairs, rate of application of pressure, etc. Find its value for several regions, including forehead, terminal phalanx of middle finger (volar surface) and back of hand.

(*c*) *Differential Threshold.*—Determine the differential threshold for some one region, say the skin of the forehead. The method to be followed may be outlined as follows:

The weights are applied in succession to the same area.

The interval between the two applications should be short (five seconds) and regular.

The duration of the stimulus must be constant.

There should be no thermal element present and visual and muscular sensations must be excluded.

FIG. 11.—Method of pithing frog.

(*d*) *Discriminative Sensibility of the Skin.*—Examine the localizing power of the same regions for which the threshold stimulus has been determined, using the older method of Weber, in which no regard is had for the individual sense spots. Note that the sensitiveness of different regions for light touch and for tactile discrimination does not vary in the same manner. Observe also the variation in the discriminative sensibility of the skin of the cheek from ear toward the lips, and of the arm from shoulder to hand.

Repeat: (*a*) After the spots have been anesthetized with ethyl chloride.

(*b*) After the spots have been anesthetized by holding a piece of ice to them.

Experiment IV.—Nerve Blocking.—*Pith a Frog.*—Expose the sciatics; test the response to electric current. Freeze a small section of the nerve with ethyl chloride and stimulate above and below the frozen areas.

Apply chloroform and ether in the same way. Results? What can you say of the action of drugs on the nerve trunks? Nerve blocking?

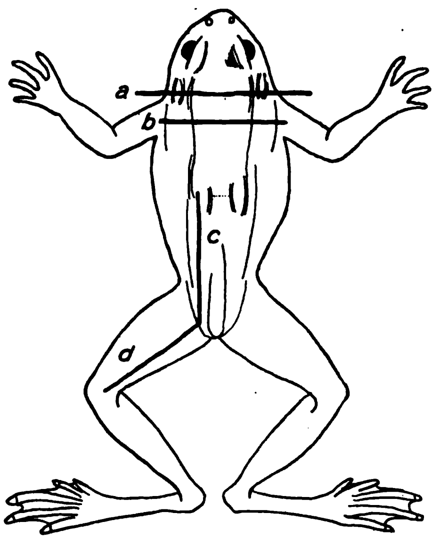


Fig. 12.—Lines showing points to cut to expose or remove. *a*, cerebrum; *b*, cerebellum; *c*, cord with sciatic; *d*, sciatic.

Experiment V.—Take a piece of filter paper 1 cm. square and soak it in a 1 per cent. cocain solution and apply it to your own tongue. Retain it in position for fifteen seconds, then test the area for sensations of touch, temperature, and taste. Contrast the sensation for quinin, sugar and salt before and after the use of cocain. Cocain in medicine is used chiefly for its local action, and this mainly to abolish pain.

Experiment VI.—Dip the foot of a frog into a 1 per cent. cocain solution. In a few minutes compare the excitability of this foot with the other, as regards response to electrical stimulation, mechanical stimulation and chemical stimulation—dipping into 1 per cent.

HCl or acetic acid. As soon as the reflex is obtained, wash off the excess of acid with water in another beaker. (Türck method of reflex time.)

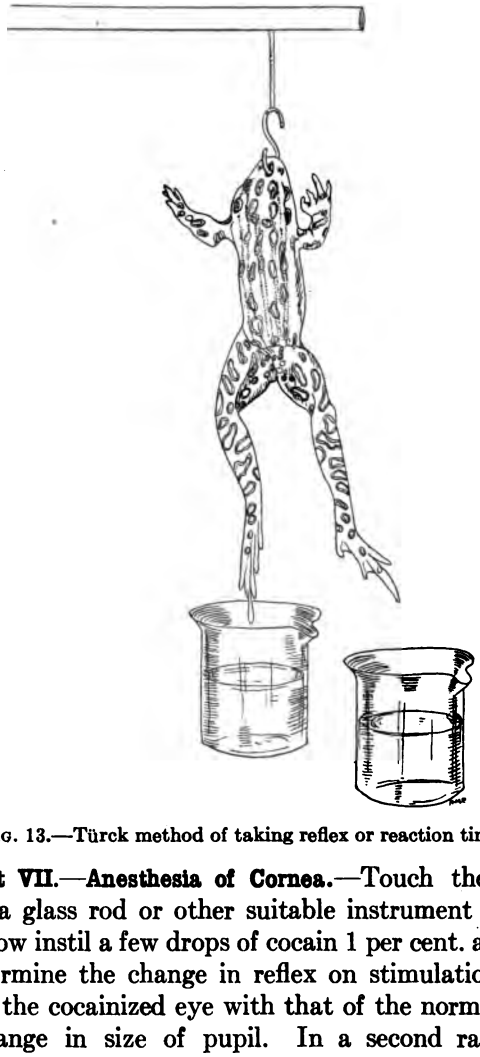


FIG. 13.—Türck method of taking reflex or reaction time.

Experiment VII.—Anesthesia of Cornea.—Touch the cornea of a rabbit with a glass rod or other suitable instrument and note the reaction. Now instil a few drops of cocain 1 per cent. and from time to time determine the change in reflex on stimulation. Compare the reflex of the cocainized eye with that of the normal eye. Note also any change in size of pupil. In a second rabbit test the anesthetic effect of quinin urea hydrochloride in the same way.

Experiment VIII.—Place one drop of the tincture of aconite on your own lip and note the sensations. A tingling scratching sensation is produced. The drugs of the aconite group are the only drugs which act on the sensory receptors when given systemically; *i. e.*, by mouth, intravenously, etc. Squibbs test for aconite is based on this action. It is as follows: Dilute 1 c.c. of the tincture of aconite

to 70 c.c. with water. Hold 4 c.c. of the diluted solution in the anterior part of the mouth for one minute and expel it. If the original tincture is of standard strength, a tingling sensation will be distinctly apparent in from ten to fifteen minutes.

Experiment IX.—Compare Experiment VIII with the result from an equal amount of the tincture of veratrin. These are the only drugs that give this reaction. How would you distinguish between the two?

DEMULCENTS.

Demulcents are colloidal substances, chiefly gums, dextrins, sugars, starches or other carbohydrate, which are used mainly to protect mucous surfaces, though they may be sometimes used on the skin. Their action is purely mechanical and protective. Bayliss has recently recommended the use by injection, of 6 per cent. gum acacia instead of physiological saline in cases of hemorrhage. The gum solution sustains blood-pressure better, and is, according to Bayliss, without harmful effects. (Note: Give distinctive characteristics of each demulcent mentioned above.)

Experiment I.—Prepare a 1 per cent. cane-sugar solution in water; also a 1 per cent. cane-sugar in 7 per cent. mucilage of acacia. Compare the taste of these. Explain.

Experiment II.—Prepare in the same way 0.1 per cent. saccharin (benzosulphonimide) in water and in mucilage of acacia or starch paste; compare taste. Explain.

Experiment III.—Reduce a sample of milk and of water to a freezing temperature and compare the temperature effect on drinking.

Experiment IV.—Prepare 1 per cent. acetic acid in water and 6 per cent. mucilage of acacia. Which tastes the more acid?

Experiment V.—Mix 2 drops of the fluidextract of nux vomica with—

1. 10 c.c. of water.
2. 10 c.c. of mucilage of acacia.
3. 10 c.c. fluid extract of glycyrrhizæ. Compare the taste of these.

Experiment VI.—Add 2 drops of a saturated solution of KI to milk and the same amount to water. Compare the taste of each. KI is best administered in milk. Is there any other advantage besides masking the taste?

1. Explain the above effects.
2. What is the philosophy of giving barley water instead of water in fevers?
3. What are the chief demulcents, their preparations and doses?

Experiment VII.—(1) Take blood-pressure of a dog by the usual method. (2) Remove one-fourth of the blood and take record of blood-pressure. (3) Inject the same volume of physiological saline and note effect on blood-pressure. (4) Repeat several times, noting the time which the blood-pressure will hold up after each saline injection. (5) After withdrawal of one-quarter the blood volume, inject an equal volume of 6 per cent. mucilage of acacia. Compare the effect of this with the action of physiological saline.

EMOLLIENTS.

Oily preparations for application chiefly to the skin. Their actions, like the demulcents, is purely mechanical, and they are used to:

- Soothe.
- Protect.
- Soften.
- Relax, and as
- Vehicles for other remedies.

They are used especially in:

- Abrasions.
- Cuts.
- Bruises.
- Chapped hands.
- Burns.
- Skin diseases, etc.

They are not often given by mouth because of their unpleasant oily taste. They are often used for eye, nose, urethra, vagina, and rectum.

The principal emollients are:

- Adeps.
- Adeps benzoinatus.
- Unguentum.
- Adeps lanæ hydrosus.
- Adeps lanæ.
- Petrolates—
    - Petrolatum liquidum.
    - Petrolatum.
    - Paraffin durum.
- Bland oils—
    - Ol. olivæ.
    - Ol. gossypii.

Ol. lini.
Unguentum aquæ rosæ.
Cera flava.
Glycerin.

1. The petrolates are not absorbed and are used to hold medicines to the surface of the skin.

2. Adeps penetrates somewhat but not so much as

3. Adeps lanæ, which is given to carry drugs through the skin. It is doubtful if these statements hold in detail.

Experiment I.—The class will be divided into groups.

Group 1. Take 1 c.c. ol. betulæ or oil of wintergreen by mouth.

Group 2. Rub 2 c.c. oil of wintergreen or ol. betulæ on the arm or other area of the skin.

Group 3. Mix 2 c.c. ol. betulæ or wintergreen thoroughly with 10 grams of petrolatum and rub on the arm as in 2.

Group 4. Mix 2 c.c. of the oil with adeps—10 grams—and repeat as in 2.

Group 5. Mix 2 c.c. with adeps lanæ hydrosus and repeat 2.

Test the urine every fifteen minutes as follows: Acidify with H_2SO_4. Add an equal volume of ether. Shake in a separatory funnel; remove the ether; add water to the ether extract, shake and add a few drops of Fe_2Cl_6. A violet color indicates salicylic acid; explain the reaction. Make a summary of results and compare.

DUSTING POWDERS.

These are protective and absorbent.

They protect from—
Air.
Clothes.
Pressure.
Friction, etc.

Any inert powder will answer as a dusting powder. The main preparations are:

Talcum purificatum—magnesium silicate.
Kaolinum—aluminum silicate.
Fullers' earth—aluminum silicate.
Terra silicea purificata—SiO_2.
Lycopodium.
Starch.
Zinc oxide.
Boric acid.

The essentials of a good dusting powder are: non-irritant, impalpable, insoluble and light. They may be mixed in any quantities, but heavy powders, like zinc oxide, should not constitute more than 20 per cent. of the weight. Examine all of the above and make a list of the best-known dusting-powder preparations.

Dusting powders are an important class of remedies and afford immense relief in cases of irritation from clothing, etc. Their simplicity, extensive use and freedom from the mysterious, to a great extent, prevents the study they deserve.

Experiment I.—Study examples of each of the above powders.

LOCAL IRRITANTS.

(Latin—*Irrito*—Excite.)

These if allowed to act long enough produce the phenomena ol inflammation, *i. e.*, redness, swelling, pain and functional change. What is the difference between irritation and stimulation?

Irritants are classified as:

1. Rubefacients.
2. Vesicants.
3. Pustulants.

This classification depends on the degree of action, rather than the drug itself. The following are the main representatives:

Rubefacients.	*Vesicants.*
Mustard.	Cantharides.
Capsicum.	Iodin.
Camphor.	Ammonia.
Ammonia.	Mustard oil.
Arnica.	Boiling water.
Alcohol.	Glacial acetic acid.
Ether.	
Chloroform.	*Pustulants.*
Iodin.	
Oil of turpentine.	Croton oil.
Volatile oils.	Tartar emetic.
Friction.	Silver nitrate.
Hot water, etc.	

Experiment I.—*Heat.*—Touch the end of a hot wire to the skin. Treatment, apply linimentum calcis; explain the action. The subject of burns is pharmacological only as the treatment involves pharmacology. Most of the treatment, after the removal of the

caustic agent when this is possible, consists at first in relieving the pain. When this is severe, morphin may be injected. In many cases the relief from pain is affected by excluding external irritants, such as air, etc. For this purpose carron oil was first used, but has now been supplanted by many modern forms of treatment, which, however, follow out the same principles. Carron oil should be sterile and care should be taken not to infect the burned surface. A coating of paraffin, which melts at a slightly higher temperature than that of the body, forms a "skin," which is said to promote healing and to prevent scar formation. Many other methods of treating burns are advocated. A saturated solution of picric acid applied on strips of sterilized gauze has been strongly recommended (Power). The tincture of iodin (Reclus), thymol iodide, 1 to 8 in vaselin, iodoform, has been recommended in the same way. A solution of sodium bicarbonate or carbonate gives relief in many cases and is said to promote healing. A saturated solution of boric acid has also been advocated. Normal saline applied on cotton has also been recommended. Dusting-powders of different kinds also have been used: acetanilid, ichthyol, resorcinol—anything to protect from the air, and at the same time act as anodynes. Immersion in water, etc. Paraffin, which melts at a temperature slightly higher than the body temperature, has at present a great vogue. It is protective, pliable and easily removable, because the dermis does not grow into it. It is somewhat painful to apply, because of the heat necessary to liquefy it; but this pain is greatly lessened by first applying liquid paraffin.

Experiment II.—Apply a drop of sulphuric acid to the skin. When it begins to sting, apply a drop of sodium carbonate or bicarbonate.

General Treatment of Burns and Scalds.—1. Remove the corrosive agent.

2. Neutralize the caustic agent.

3. Linimentum calcis, liquid petrolatum or other emollient, to exclude air or irritants.

4. Special treatment.

5. Symptomatic treatment.

Experiment III.—Apply 5 per cent. phenol to the skin until it is white. Immediately transfer to alcohol or glycerin. Explain the whitening and the antidotal effect. Phenol is much more soluble in alcohol and glycerin than it is in protoplasm. It is not advisable to dip the finger into phenol. If by any chance the antidote is not effective, the removal of the skin from the entire circumference of the finger or limb, no matter how small, may be a serious affair.

Experiment IV.—Anesthetize a dog and introduce 50 c.c. of phenol or $HgCl_2$ or other corrosive into the stomach (Fig. 1 and 14). When the animal dies or is killed, make a complete postmortem. How would you treat a case of poisoning by phenol or corrosive sublimate? Any corrosive? It may be best to leave this experiment until the end of some experiment in which a dog is used, and as a final experiment administer one of these poisons.

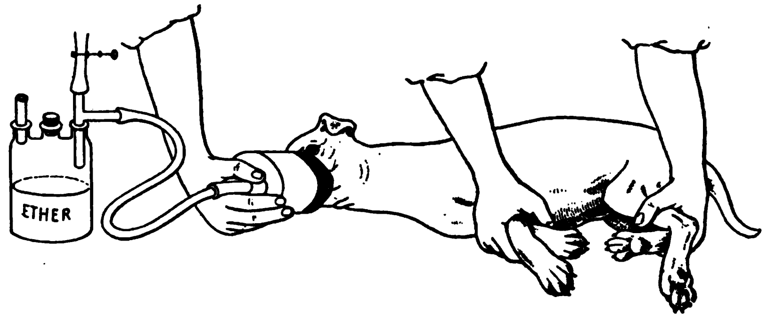


Fig. 14.—The cone method of anesthetizing a dog. The amount of ether and air may be regulated by the screw clamp and the glass tube in the ether bottle

Experiments V.—*Irritant Emetics.*—With the exception of apomorphin, all the commonly used emetics act chiefly by peripheral irritation. Give a dog 50 c.c. 1 per cent. $CuSO_4$ by a stomach tube. (See Fig. 7.) $ZnSO_4$, ipecac, mustard, etc., act similarly. (See Emetics.)

Experiments VI.—Irritants may be compared by placing them on a limited area of the skin and covering them with a capsule, beaker, etc., or with adhesive plaster. Cut several pieces of adhesive plaster about one inch square. Place a drop or its equivalent of the following rubefacients on it and apply to the skin:

1. Croton oil.
2. Ceratum cantharides.
3. Oil of turpentine.
4. Ammonia.
5. Mustard plaster.
6. Oleoresin of capsicum.

Keep these in place for from thirty minutes to two hours and compare the intensity of the action. Do not let them remain long enough to blister. If this happens, see treatment of burns and scalds.

Experiments VII.—Remote action of rubefacients. Take the respiration, pulse-rate and blood-pressure of a student while in a

horizontal position. Remain in the position and apply a turpentine stupe to the abdomen. What is the effect on the heart, respiration, etc.?

This may be repeated on different students with chloroform, ammonia, liniment, mustard plaster, etc. Keep a record of the time elapsing between the application and the result.

Experiment VIII.—Count the heart-rate and respiration in a rabbit. Let it inhale ammonia, ether, etc., and record the action on the heart and respiration. Explain the nervous pathways involved in the effect.

Experiment IX.—Paint some tincture of iodin on the skin and compare the sensation with the effect when it is applied on the mucous membrane inside the lip.

Experiment X.—Place a drop or two of chloroform on the back of the hand. On the other place the same amount and cover it with a crucible or small beaker. What is the difference in the sensation? What harmful effects may result from covering an area tightly to which chloroform liniment or ammonia has been applied.

Skin Irritants and Rubefacients.—**Experiment XI.**—Mix a tablespoonful of mustard flour and four times its volume of wheat flour with a little water at 40° C. Spread this on a piece of cloth and place a piece of muslin over the mixture on the cloth. Apply to the skin over the stomach and cover with a cloth. Study the sensation until the irritation becomes marked. Take the pulse and respiration-rate before and after the application. This is often used as a domestic remedy in cases of colic, etc. It is valuable as a remedial agent when properly used, but often causes burns which become infected and for this reason must be used with great care.

Experiment XII.—Apply one drop of chloroform to the arm and cover with a watch-glass or with the mouth of a bottle. Linimentum chloroformi is used as a rubefacient.

Experiment XIII.—Apply emplastrum cantharidis 2″ x 2″ to the skin as in Experiment II.

Experiment XIV.—Snuff 1 grain of a mixture of saponin, in starch, 1000. Do not take more than 1 grain of the mixture.

Experiment XV.—Give a cat 1 c.c. per kilo of saponin, 1 to 1000, by means of a stomach tube. Observe and record the results for an hour. Discuss the results obtained.

Steps in the Actions of Irritants.—First: *Tissue Injury to Some Degree.*—It may be slight or severe.

Second: *Reaction of the Body to the Injury:*

1. Capillaries and small vessels dilate, causing redness.

2. The vessels lose their tone and a filtration of serum into the region produces edema and swelling.

3. The tension of the edema and swelling, pressing on the nerves, causes pain. The nerves are also sensitized by toxins.

4. Leukocytes in the region may disintegrate, forming pus.

5. Each of the foregoing operates to cause change in function—emesis, lameness, etc., depending on the location of the injury.

6. If the disintegration of tissue is great enough, the products derange the heat regulating centers, and an increased temperature results.

7. If the disintegration of tissue be considerable, scars and cicatrices may result and any complication between restoration and exitus.

CAUSTICS OR ESCHAROTICS.

These are drugs which destroy the tissues to which they are applied. They are used:

1. To disinfect wounds, bites of animals, etc.—phenol, potassium permanganate, hydrogen peroxide, tincture of iodin, etc.

2. To remove warts, polypi, etc., HNO_3, H_2SO_4, trichloracetic acid, $AgNO_3$ chromic acid, etc.

3. To remove hair-depilatories; sometimes used also in tumors, neuralgias, etc. The action is chemical or physicochemical. They precipitate, dissolve, or hydrolyze the proteins of the tissues.

Experiment I.—To a solution of the white of an egg in water, add in a series of test-tubes, drop by drop, $AgNO_3$, Fe_2Cl_6, $HgCl_2$, $Pb(C_2H_3O_2)_2$, $CH_3.COOH$, HCl, H_2SO_4, $NaOH$, KOH. Note the condition of the precipitate, whether granular, slimy or flocculent. Add an excess of the reagent and note the results. Query: Which of the above, acid, alkali, or salt, would cause the deepest corrosion? Why? What influence would the acid radical have on the action to a corrosive salt? Why has a slight burn with an acid a shrivelled astringent appearance and feeling while that of an alkali has a slimy feeling?

Experiment II.—Subject small pieces of muscle, skin, etc., to the action of these corrosives. Note the difference in appearances and feeling. Dip the fingers into 5 per cent. acetic acid, and compare with 5 per cent. NaOH. What is the antidote and treatment for poisoning by each of the above? Give the symptoms of each and an explanation of the cause of each symptom.

Experiment III.—*Demonstration.* Select three dogs and give:

1. 100 milligrams per kilo of mercuric chloride by stomach tube.

2. 100 c.c. 10 per cent. nitric acid.

3. 100 c.c. 10 per cent. caustic soda solution.

Compare the symptoms carefully and when animals seem in danger, apply the proper treatment. At the end of the period, kill the animals with chloroform and hold postmortem. Compare the gastro-intestinal tracts of the three. For the postmortem appearances, other animals may be used which are anesthetized throughout the experiment. Experiments of this kind may be done at the end of other experiments.

Symptoms and Treatment of Caustic Poisoning.—*Action on the Alimentary Canal.*—The introduction of caustics into the mouth is either due to accident or suicidal intent. The symptoms are: Pain, nausea, vomiting, diarrhea, tenesmus, etc., anxiety, vertigo, delirium, convulsions and collapse. The heart and respiration may be stimulated at first, but soon become weakened and fade away. The symptoms are the same for almost all irritants or caustics. Variations are not pathognomonic.

General Principles of Treatment.—1. Neutralize and remove the caustic if possible.

2. Dilute, give water or milk, or other diluent in abundance. This is given for two reasons: (*a*) to dilute and therefore lessen the corrosive action, since the caustic effect is proportional to the concentration; (*b*) dilution favors removal of the poison.

3. Wash out the stomach, using stomach-tube if it is thought the corrosive action has not gone far enough to make perforation of the alimentary tract with the stomach tube a probability. The use of demulcent preparations like diluted starch solutions, milk, etc., are pleasant to the corroded surfaces.

4. Give antidotes: Chemical or physiological as are indicated.

5. Sustain patient by symptomatic treatment—heat if necessary, or cold applications if desirable. Special treatment as indicated.

CHAPTER III.

PHARMACOLOGY OF THE GASTRO-INTESTINAL TRACT.

THE local action of drugs on the intestine:

(*A*) *Specific Irritants of the Gastro-intestinal Tract:*

These may be classified as:

1. Stomachics, or Bitters.
2. Carminatives.
3. Emetics.
4. Cathartics or Purgatives.

(*B*) *Gastro-intestinal Sedatives:*

Obstipants or Astringents.

(*C*) *Drugs Acting on Intestinal Flora and Fauna:*

1. Anthelmintics.
2. Intestinal disinfectants. With these general disinfectants may be studied.

BITTERS.

These have nothing in common, except the bitter taste. As a group, they are characterized by their bitter or aromatic taste.

Classification:

1. Simple.
2. Aromatic.
3. Astringent.
4. Compound.

1. **Simple Bitters.**—A bitter taste is all that characterizes these. They contain practically no tannin nor volatile oil. They can therefore be used with iron preparations or salt solutions. *They are miscible with water.*

Action of Iron on Tannin? Salts on Oils?

The Chief Simple Bitters are:

Calumba.
Quassia.
Taraxacum.
Gentiana.
Chirata.
Xanthoxylum.

Weak preparations of *nux vomica, quinin, strychnin,* etc., may be used for the same purpose.

2. **Aromatic Bitters.**—These contain aromatic oils and bitter principles but no tannin. They can, therefore, be used with Fe preparations.

Their alcoholic preparations cannot be mixed with water.

Principal Aromatic Bitters:

Calamus-sweet flag.
Aurantii amarii cortex.
Absinthe.
Humulus.

3. **Astringent Bitters.**—Tannin is the prominent ingredient. Volatile oils may be present in small amounts. *The preparations may be mixed with water. They are, however, incompatible with Fe.*

Principal Astringent Bitters:

Cinchona.
Serpentaria.
Cimicifuga.

4. **Compound Bitters.**—These are blends of the other preparations. Blending improves them. In most cases, these should be given the preference. Whether or not they may be mixed with water depends on the choice of the mixture.

Principal Compound Bitters:

1. Tinctura gentianæ composita, U. S. P. This contains no tannin, but the coloring matter darkens with iron.
2. Tinctura cinchonæ composita, U. S. P.
3. Elixir gentianæ, N. F.

Physiological action of the Simple Bitters:

These are classified under the *locally* acting drugs. They are administered by mouth, and their only action is on the *alimentary tract.* However, some of their action may be psychic. One of the principal reasons for their administration is to increase the appetite and digestion. Digestion, however, has a large psychic element.

Local Action.—*Mouth.*—All sensory nerves connect, directly or indirectly, with all motor nerves. Hence, smell, sight, thought of food, contact with food or drugs, movements of jaw may cause a flow of saliva. Taste reflex may cause a flow via gustatory nerve to the *salivary center* in the medulla, and via the *chorda* and *sympathetic to the glands.*

Gastric Secretion.—1. Bitters cause less immediate secretion on an empty stomach than does an equal volume of water.

2. Thirty minutes later, however, secretion is greatly increased.

This increase diminishes and ceases after two hours. Hence, the reason for giving bitters half an hour before meals.

3. The peptic glands show histological evidence of activity. (Brekai.)

4. The leukocytes in the blood are increased by bitters in the stomach. Leukocytes very probably aid in absorption.

5. Bitters increase the gastric secretion before a Pavlov meal, and this taste reflex may explain the whole action of bitters. (Cushny.)

6. Gastric secretion is also influenced by events taking place at a distance, and by psychic events. In a boy, whose esophagus was closed by drinking lye, the sight and smell of food caused secretion of gastric juice. Sham feeding, sight, etc., have a great effect.

Nerves Involved in the Secretion of Gastric Juice:

1. Cutting the splanchnics has no effect.
2. If the Vagus be cut secretion stops (atropin).
3. After allowing time—three or four days—for the constrictors to degenerate, stimulation of the cut end of the vagus, gives secretion—the vagus therefore is the secretory nerve. Hormones or chemical secretogogues also play a part.

Therapeutic Uses of the Simple Bitters:

1. To increase the appetite and promote digestion.
2. In Convalescence.
3. In Dyspeptics.
4. In Neurasthenia.
5. Quassia as in *infusion* is given as an enema in cases of pin worms.

Experiment I.—Compare the taste of each of the bitters mentioned above.

Experiment II.—Mix tincture of ferric chloride with a member of each class of bitters.

Experiment III.—In a dog with a gastric fistula, take a tracing of the stomach contractions without anesthesia, and while the tracing is being taken place a few drops of a bitter in the animal's mouth. See Fig 15.

Experiment IV.—In a dog with a Pavlov fistula, collect the normal secretion for thirty minutes. Now give 2 c.c. of tincture of gentian by mouth and again collect for thirty minutes.

Experiment V.—For three successive days, each student should take 6 c.c. of tinctura gentianæ composita, in a glass of water, thirty minutes before each meal. A record of the general feeling and appetite should be kept. The three following days take 30 c.c.

syrupus sarsaparillæ compositus in the same way and compare the effect produced by the bitter with that produced by the syrup. If groups of students are living together the two series may be run simultaneously.

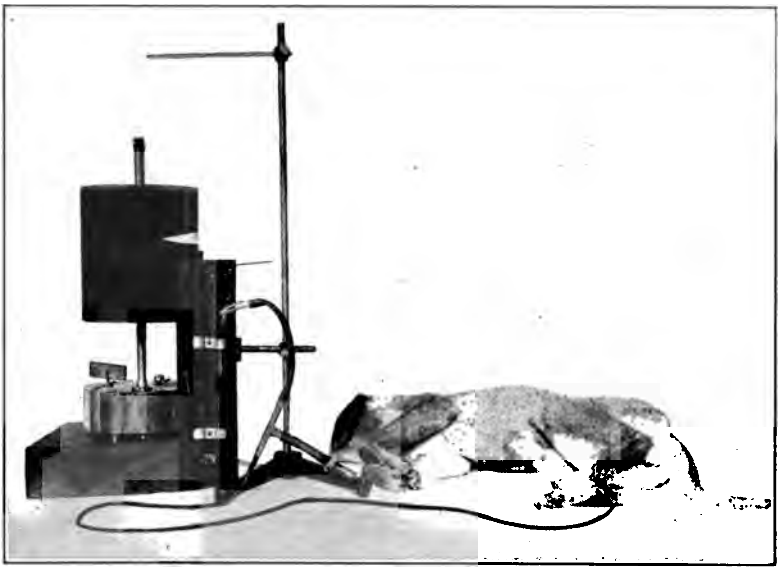


FIG. 15.—Method of recording stomach contractions. A water manometer is used. The float is made of a phenolsulphonephthalein ampoule and the tube to the stomach ends in a soft-rubber thimble of very light rubber. The side tube with screw clamp permits a slight amount of pressure to be introduced.

CARMINATIVES.

These are the agents which aid or stimulate the expulsion of gas from the gastro-intestinal tract. They thus prevent flatulency or the distention of the stomach or intestines with gas. The active ingredient is usually a volatile oil or resinous principle. Other carminative bodies are ether, chloroform, ammonia, carbon dioxide, etc. Carminatives have the following properties:

1. Antiseptic and anodyne, *e. g.*, oils of eucalyptus, cloves and cinnamon, are used in tooth cavities in cases of toothache.

2. They are general protoplasmic irritants, so that when rubbed on the skin they are rubefacients.

Volatile Oils.—Main actions of volatile oils:

1. Mildly antiseptic—characteristic of benzene derivatives.
2. Irritant and rubifacient.
3. Carminative and anodyne.

They are used mainly as:

1. Carminatives.
2. Flavoring agents.
3. Genito-urinary antiseptics.

Experiment I.—Examine and taste various specimens. This will best be accomplished by saturating water with the oils and then by tasting the water. Use any volatile oil.

Experiment II.—Place a drop of a fixed oil and a drop of a volatile oil on white sized paper, dry at 40° C. and compare.

Experiment III.—Heat a drop of a fixed oil in a test-tube with $KHSO_4$ over a free flame. (Compare odor with a volatile oil treated in the same way.)

Experiment IV.—Swallow a drop or two of any volatile oil on sugar. What is the feeling?

Experiment V.—Volatile oils are excreted in the urine, to which they often impart definite odors. They are also excreted by the lungs. When drugs are taken by the stomach it is difficult to tell whether or not they are excreted by the lungs because the odor may come up by way of the esophagus. To show that they may be excreted by the lungs, anesthetize a dog and take blood-pressure tracings. Insert a cannula into the trachea and inject 1 c.c. of any volatile oil into the femoral vein. (Note the odor of the exhalation in the tracheal cannula.) Connect the tracheal cannula with a bottle of water and see if enough oil is exhaled to impart an odor to the water. Does this eliminate excretion through the esophagus?

Experiment VI.—Large doses of any volatile oil may cause convulsions. Absinthe acts decidedly on the nervous system after the prolonged use of small doses. Stearoptenes also act as the volatile oils. Administer 10 c.c. per kilo of 20 per cent. camphor in oil, by means of a stomach tube, to a rabbit or inject one-half this amount intraperitoneally. Note the peculiar "bucking" type of the spasm.

Experiment VII.—Each student can test at least two of the following by rubbing some of the drug on the forearm: Oil of turpentine, oil of peppermint, menthol, 2 per cent., dissolved in alcohol, chloroform, ether, or spiritus ammoniæ aromaticus. Now, instead of rubbing, place a few drops on the skin and cover tightly with a capsule, crucible or other device to exclude the air.

Experiment VIII.—Anesthetize a rabbit, cat or small dog. Take respiration and blood-pressure tracings. Inject 20 c.c. per kilo of 20 per cent. camphor in oil into the peritoneum. Keep the anesthesia uniform and note the action on the heart and respiration.

Experiment IX.—Compare the action of camphor (Experiment VIII) with the following: Inject hypodermically 1 c.c. per kilo of 0.1 per cent. solution of veratrin. Repeat in twenty minutes if necessary.

Experiment X.—Fill six fermentation tubes with 5 per cent. dextrose solution containing yeast. Keep one for a control and to the others add 1, 2, 3, 5 and 10 drops of oil of turpentine. Shake and place in an incubator at 40° C. and note changes every 15 minutes for 3 hours.

Experiment XI.—Repeat experiment X, using oil of cloves, 10 per cent. thymol in alcohol, chloroform, oil of peppermint, oil of cinnamon.

Experiment XII.—Fill a series of small bottles with urine. Keep one as a control and treat the others with the above volatile oils (1 c.c. volatile oil to 100 c.c. of urine). Set in a warm place and note the odor twenty-four and forty-eight hours later.

Experiment XIII.—Separate students may take 1 or 2 drops of one or more of the following drugs on a lump of sugar: Oil of turpentine, oil of peppermint, 2 per cent. menthol dissolved in alcohol; ether, 1 c.c.; chloroform, ½ c.c., spiritus ammoniæ aromaticus, 2 c.c. in water. Is there any action on heart-rate or respiration? Have they a carminative action?

Experiment XIV.—Take 0.3 c.c. eucalyptol, 0.3 gram menthol, 30 c.c. light liquid petrolatum and mix. Use as a spray for the nose. (Results?)

Experiment XV.—Test the solubility of volatile oils in alcohol, ether, chloroform and fixed oils. Compare and discuss volatile oils and fixed oils from the point of view of:

1. Their chemistry.
2. Their physical properties.
3. Their economic uses.
4. Their therapeutic uses and
5. Their fate in the body.

The following are the main therapeutic uses of volatile oils and other carminatives arranged from Bastedo (*Pharmacology and Therapeutics*).

1. As anticolics (in intestinal and uterine cramps): Anise, peppermint, dill water, distilled liquor, essence of ginger, spirit of peppermint, aromatic spirit of ammonia, and Hoffmann's anodyne.

2. As odors and flavors: Anise, bitter almond, caraway, cinnamon coriander, fennel, lavender flowers, lemon, nutmeg, orange peel, peppermint, spearmint, rose and vanilla.

3. As correctives of irritant cathartics: Oils of anise, caraway, cloves, coriander, fennel and peppermint.

4. For tympanites (as in typhoid fever, pneumonia or following operations): By mouth, oil of turpentine or asafetida, in pill or tincture; by rectum, oil of turpentine, tincture of asafetida, added to a soapsuds enema.

5. As anthelmintics: Oil of chenopodium for round- and hookworms; thymol for hookworms.

6. As stimulants to mucous membranes of nose and throat: Eucalyptol, camphor and menthol, about 1 per cent. of each mixed, with light liquid petrolatum, and used as a spray.

7. As antiseptics and anodynes: Oil of cloves or oil of cinnamon, in a decayed tooth, a drop on cotton.

8. As counterirritants: Camphor, capsicum and menthol, and the oils of mustard and turpentine.

9. As stimulants in chronic skin diseases, such as eczema, psoriasis, etc.: The oils of cade and tar in the form of an ointment.

10. As stimulants to the growth of hair: Oil of mace.

11. As antirheumatics: Methyl salicylate in the form of oil of birch or wintergreen. Also used externally as a liniment.

12. As antihysterics: Asafetida, camphor, musk, sumbul and valerian.

13. As anti-asthmatics: Powdered cubebs smoked in cigarette form.

14. As bronchial stimulants: Creosote, oil of turpentine, terebene, syrup of tar.

15. As diuretics: Spirit of juniper; fluidextract of buchu and uva ursi.

EMETICS.

Experiment I.—Give a dog 1 c.c. per kilo of 0.1 per cent. solution of apomorphin hydrochloride by stomach tube. Repeat every ten minutes until emesis occurs. Record the amount and the time required to produce vomiting.

Experiment II.—Give the same amount as in Experiment I subcutaneously and record as in Experiment I.

Experiment III.—Inject one-half of the amount into the femoral vein without an anesthetic; compare Experiments I, II and III and also the following.

Experiment IV.—Give a dog 50 c.c. 1 per cent. $CuSO_4$ by stomach tube. Note that there is little nausea or depression. *Cf.* Experiments I, II and III.

Experiment V.—Using another dog compare the effect of the same strength and amount of $ZnSO_4$, 50 c.c. 1 per cent.

Experiment VI.—Tartar emetic; give a dog in the same way 5 c.c. per kilo 0.1 per cent. tartar emetic. Compare nausea and depression with that produced in the preceding experiments.

Experiment VII.—Ipecac; give by stomach tube 0.25 c.c. of the fluidextract per kilo body weight in 50 c.c. water.

Experiment VIII.—Anesthetize a dog with chloroform or ether and give twice the amount of apomorphin as in Experiment I. After fifteen minutes remove the anesthetic. Record results.

Experiment IX.—Give a dog a hypodermic of 2 c.c. of 3 per cent. morphin. Repeat dose in fifteen minutes. After thirty minutes repeat Experiment I.

Experiment X.—Many other substances cause vomiting when injected intravenously in the unanesthetized dog, while they may be without effect on the anesthetized animal. The following will cause vomiting.

(*a*) 5 c.c. of 5 per cent. peptone solution.

(*b*) 1 mg. per kilo body weight of digitoxin.

(*c*) 100 mg. per kilo of digitalis.

According to Hatcher, this acts on the vomiting center because it will cause vomiting in the eviscerated animal.

What are the proofs that apomorphin acts directly on the vomiting center? (*b*) Give proofs that $CuSO_4$ acts peripherally.

PURGATIVES OR CATHARTICS.

Purgatives are drugs which cause or hasten evacuation of the contents of the bowel.

Classification of Cathartics:

1. Chemical.
2. Therapeutic.

Chemical:

Inorganic:

1. Salines, sulphates, phosphates, citrates.
2. Sulphur.
3. Mercurials.

Organic:

1. Purgative oils, castor and croton.
2. Anthracene derivatives.
3. Resinous anhydride or jalap group.
4. Phenolphthalein.

5. Colloid and emollient laxatives.
   - Agar-agar.
   - Liquid petroleum.
   - Manna.
   - Fruits, etc.

Study the mechanism of the action. Is the site of action on the small gut, the large gut or on the entire tract?

Therapeutic Classification:

1. Aperients.
2. Laxatives.
3. Eccoproctics.
4. Cathartics.
5. Purgatives.
6. Cholagogues.
7. Hydrogogues.
8. Drastics.

Discuss the advantages and limitations of each classification; also discuss the mechanism of the action, the origin of the fluid, the difference between colic and inflammation of the gut, and the uses and abuses of cathartics. Besides the use of drugs, non-pharmacal measures may be used to restore adequate or normal bowel movements. The cathartics should be used only when necessary, since the aim should be to use drugs temporarily.

Non-pharmacal Measures:

1. Habit formation of the evacuation of the bowel reflexes by a regular time for stool, persistently carried out.

2. An immediate response to the desire to defecate since, if this is not obeyed constipation habits are forced on the gut.

3. Exercise is of the greatest value in developing and sustaining the tone of the muscles and nerves and keeping them in a responsive condition, through better circulation.

4. Massage of the intestines, either normal or with the aid of a ball or roller, working in the direction of the bowel movements. This, however, cannot replace exercise but may act as an adjuvant to exercise.

5. Diet properly selected, to give a large residue, such as vegetables, whole wheat, oatmeal and other cellulose containing foods. The bowel needs a certain amount of "roughage," since it must have exercise as any other organ.

Demonstration of the influence of concentration on the action of a purgative.

Experiment I.—1. Keep two dogs without food or water for twenty-four hours.

2. Then administer to one 3 c.c. of 35 per cent. sodium sulphate per kilo body weight and place in a cage for observation.

3. To the other give 25 c.c. of water per kilo of body weight. After an hour give 3 c.c. of 35 per cent. sodium sulphate per kilo and in addition 200 c.c. of water. (Compare the cathartic action of the salt in this dilute form with that of Dog 1, in which the concentrated solution was used.)

Experiment II.—*Action of Cathartics on Man.*—Cathartics are perhaps the most important and most used group of drugs. For this reason during the course each student should take one of the following cathartics each week, until all have been taken and keep record of the color, consistence, size and number of stools, griping, etc. Valuable information regarding the action of cathartics can be obtained in this way that can be obtained in no other way.

(*a*) Pilulæ aloes, 2 pills.

(*b*) Calomel, 0.06 gram and repeat in two hours.

(*c*) Aromatic fluidextract cascara sagrada, 4 c.c.

(*d*) Epsom salts, 20 gm. in a glass of water followed at once by another glass of water only.

(*e*) Castor oil, 15 to 25 c.c.

(*f*) Petrolatum liquidum, 30 c.c.

(*g*) Phenolphthaleinum, 0.2 gm.

(*h*) Resina padophyllum, 0.01.

(*i*) Syrupus sennæ, 8 c.c.

(*j*) Jalap, 1 gm.

For comparison all of these had best be taken in the evening or at bedtime.

Experiment III.—*Moreau Loop Experiment.*—Use physiological salt solution in the middle loop and any of the other cathartic solutions in the other two. Make at least three loops as follows:

Anesthetize a dog with ether. Expose the intestines by an incision along the linea alba. Handle with extreme care and keep them warm, so that absorption is as nearly normal as possible. Isolate along loop of the small intestine as near the large intestine as possible. Ligate this at the upper end and carefully squeeze the contents toward the large gut. Now divide the emptied small intestine into segments of exactly three or four inches in length. Each segment must be exactly the same length. Place 10 c.c. physiological saline in the middle loop. Do this without injuring the gut. Place the same amount of any of the other solutions mentioned below in the loops on each side of the saline loop.

CATHARTICS.

These diagrams are intended to show the different ways in which cathartics may act.

It is not possible to classify strictly, as the action of some is too extensive to be limited to one group or illustrated by a single diagram.

The numbers indicate the diagrams that represent what is believed to be the most prominent action in case of each drug, without intending to show the complete action in every instance.

Group A. LAXATIVES.

Fruits. (1)
Sugar.
Sulphur.
Purges in small doses.
Glycerin (by enema). (2)

Group B. PURGES.

Anthracenes. (1)
Aloe. (1)
Mercurials. (4) (5)
Oleum Ricini. (3) (4)
Rhamnus Frangula. (1)
Cascara Sagrada. (1)
Rheum. (1)
Magnesia. (3)
Senna. (1)

Group C. HYDRAGOGUES.

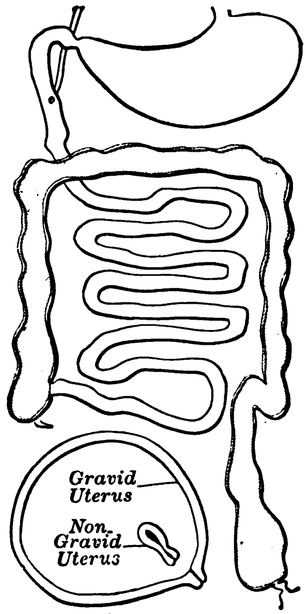
Salines.

Magnesii Citras. (3)
Magnesii Sulphas. (3)
Potassii Bitartras. (3)
Potassii et Sodii Tartras. (3)
Sodii Phosphas. (3)
Sodii Sulphas. (3)
Elaterinum. (4)
Jalapa. (4)
Senna. (1) (4)

Group D. DRASTICS.

Colocynthis. (5)
Elaterinum. (3) (4) (5)
Jalapa. (3) (4)
Cambogia. (5)
Oleum Tiglii. (5)
Podophyllum. (5)
Scammonium. (5)
Resins. (5)

The red color shows the site of action, and indicates stimulation of motility or secretion.



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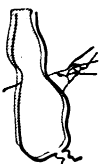

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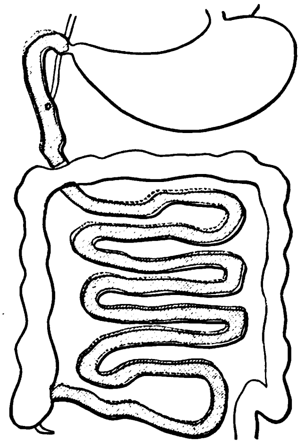
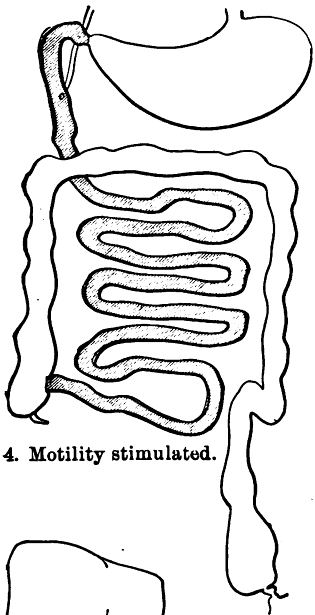
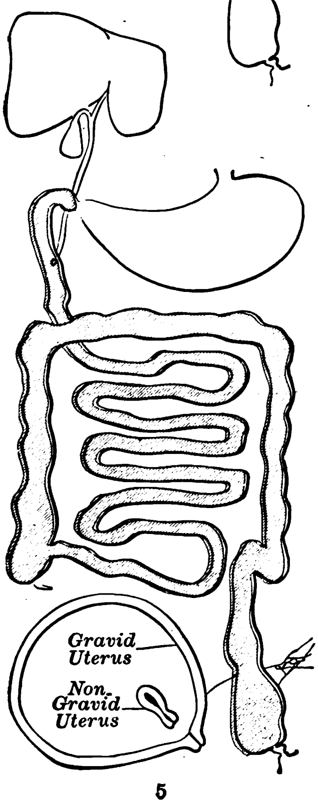


3. Secretion stimulated.

PLATE I.



4. Motility stimulated.



5

CATHARTICS.

The natural provision for intestinal evacuation includes three factors:

First. A certain amount of indigestible matter in the food.

Second. Peristaltic motion from the stomach downward.

Third. A certain degree of fluidity of contents.

A decrease of any one factor tends to constipation, while an increase tends to diarrhœa.

Cathartics act by influencing these several factors.

Laxative foods act by reason of their indigestible residue. Almost any cathartic may have simply a laxative effect when used in small doses.

Purges, by their irritating action, stimulate peristalsis, the milder ones acting mainly upon the large intestine (1). Some, in large doses, approach drastics in severity of action (5). The absence of bile diminishes the activity of podophyllum, jalapa, rheum, senna, and scammonium.

Hydragogues act in two ways:

The less irritating *salines* cause a marked increase of fluid by determining a flow of serum from the blood into the intestine (3). A low blood-pressure diminishes their activity.

The more irritating hydragogues stimulate very promptly peristalsis of the small intestine, with the result that the fluid contents are hurried onward and absorption is lessened (4). Secretion also may be increased. Copious liquid stools result.

Drastics stimulate powerfully the peristaltic movement of the whole tract (5), causing prompt, frequent stools, with severe griping. In large doses they act as irritant poisons, and may cause contractions in the gravid uterus.

Cholagogues favor the flow of bile into the duodenum, probably through the increased peristalsis. The influence of cathartics upon the function of the liver seems uncertain and indirect.

The red color shows the site of action, and indicates stimulation of motility or secretion.

(*a*) 20 per cent. magnesium sulphate.
(*b*) 20 per cent. sodium phosphate.
(*c*) 10 c.c. castor oil containing two drops of croton oil.
(*d*) Fluidextract of rhubarb.
(*e*) Fluidextract of senna.
(*f*) 10 per cent. solution of phenolphthalein.
(*g*) Liquid paraffin.

At the end of two hours carefully collect the fluid in the loops and measure it.

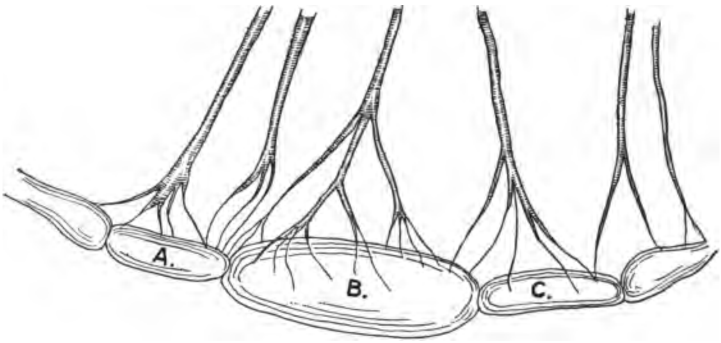


FIG. 16.—Moreau loop method of studying the absorption of liquids—especially cathartics—from the intestine.

Compare Results.—If several groups are doing this experiment, water, sugar solutions, serum, etc., may be added to the list and the results of each group tabulated.

While waiting for the two hours to pass, blood-pressure experiments, like epinephrin, may be carried out on these animals.

Experiment IV.—All cathartic salts precipitate calcium. To a solution of calcium chloride, in a series of test-tubes, add a few drops of:

(*a*) Magnesium sulphate.
(*b*) Sodium phosphate.
(*c*) Sodium citrate.
(*d*) Sodium and potassium tartrate.

Calcium, therefore, has an anticathartic or obstipant action.

Attempts have been made to find centrally acting cathartics, but so far no practical, centrally acting cathartic has been found.

OBSTIPANTS OR ASTRINGENTS.

Obstipants have the opposite action of cathartics and are used when the movements of the bowel are too frequent, or are painful

because of griping. They are in the main locally acting drugs. They are classified as

1. Acids: Tannic acid and tannin, tannalbin, tannigen, etc.
2. Metallic Salts: Bismuth and cerium salts, lead acetate, alum, silver nitrate, ferric chloride, etc.
3. Bases or alkalies: Calcium hydroxide.
4. Alkaloids: Atropin, morphin.
5. Inert Powders: Charcoal, talcum, etc.

Acids.—Tannin or tannic acid is the astringent principle of all plants. It acts:

1. By precipitating proteins within the gut and rendering it less irritable.
2. By direct action on the gut, causing a constriction and possible covering of the sensory nerves by a constriction of the surfaces over them.
3. By forming a mechanical coating or precipitate over the surface. In all cases they lessen the sensitivity of the gut or nerves, and leave the nerves less exposed to the action of irritating products in the gut.

The chief vegetable astringents are:

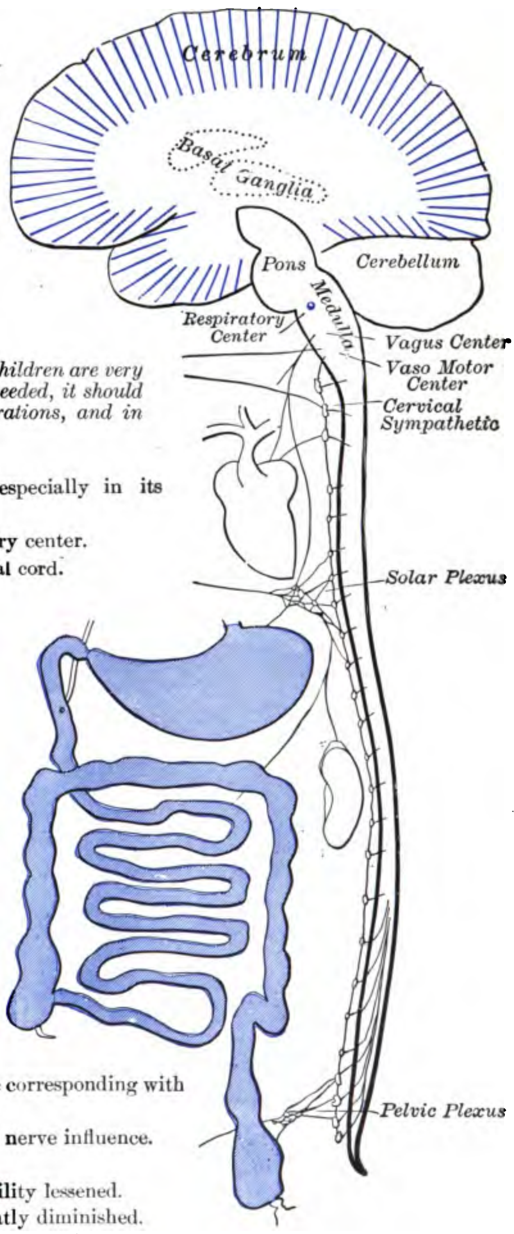
Acidum tannicum: dose, ½ to 1 gram.
Tinctura gambir composita: dose, 2 to 4 c.c.
Tinctura kino: dose, 2 to 4 c.c.
Extractum krameriæ: dose, 2 to 4 c.c.

Metallic Salts.—Bismuth subnitrate or subcarbonate are most used. Their action is believed to be chiefly mechanical, acting as a dusting-powder to the intestine and so protecting it from irritation. There may also be some astringent and absorbent effect. These salts were formerly used by roentgenologists for the purpose of photographing the gastro-intestinal tract, but they have largely been supplanted by barium sulphate.

Ferrous sulphate, tinctura ferri chloridi, have been used to some extent in diarrhea. Alum has also been used; also silver nitrate. All of these, however, are slightly irritating, and at the present time are used more as local styptics.

Calcium Hydroxide.—Chiefly used in the form of liquor calcis, which contains 0.15 per cent. $Ca(OH)_2$. Calcium acts as an obstipant by neutralizing the acid product in the intestine, by lessening the excitability of the sympathetic system, by a direct depressing effect on the muscle and by lessening of the permeability of the capillaries. In case of children, when lime water is mixed with the milk, clotting in the stomach is modified and the clots are smaller,

MORPHINE.



In form of SULPHATE, ACETATE, or HYDROCHLORIDE. Gr. $\frac{1}{8}$–$\frac{1}{4}$ (Gm. .008–.015).

Classified as:

Anodyne. Narcotic.

Physiologic action:

The action of morphine is essentially that of a central nerve depressant, the local action of the drug, wherever applied, being almost *nil* except on the gastro-intestinal tract. *Children are very sensitive to this drug, and, if needed, it should be used in the weakest preparations, and in less than the proportional dose.*

Nervous System.

Brain. Depresses cerebrum, especially in its higher intellectual functions.

Medulla. Depresses respiratory center.

Spinal Cord. Stimulates spinal cord.

Nerves. The peripheral nerves are not affected by ordinary doses.

Muscular System. Not affected by ordinary doses.

Circulation. Not much influenced by ordinary doses.

Heart. Opinions differ. Any influence of a moderate dose must be slight and probably indirect. Large doses slow the heart by stimulating inhibition.

Capillary area. Not much influenced, except that the cutaneous area of the head and neck may show dilatation.

Respiration. Depressed to a degree corresponding with size of dose.

Eye. Pupils contracted by central nerve influence.

Digestive System.

Stomach. Secretion and motility lessened.

Intestines. Peristalsis is greatly diminished.

Elimination. Secretions generally are diminished, except the perspiration. The drug is partly changed in the system, but the greater part is eliminated by the gastro-intestinal tract.

and more easily digested. Its action on intestinal movement can readily be seen either by direct application or by intravenous injection.

Alkaloids.—The alkaloids that tend to cause obstipation are the opium alkaloids—especially morphin—and atropin. Morphin acts on the peripheral nervous mechanism, since Magnus found that it exerted its constipating action after all the nerves were cut. The movement of the gut is lessened. Large doses in the cat and dog cause violent peristalsis and diarrhea, followed by a constipating effect. The increased peristalsis never occurs in man.

Atropin.—Atropin lessens the movements of the gut in a way not yet understood. It was formerly taught that it paralyzed the autonomic vagus endings, but Magnus has found that stimulation of the vagus is still active after atropin. He found that therapeutic doses lessen peristalsis, while larger doses increase the movements. It is probable, judging from the action of atropin in other locations, that the action is a paralytic one on the autonomic endings; and that the sympathetic and autonomic fibers are not so distinct in this region as is taught in most books.

Inert Powders.—Talcum and charcoal or any other inert powder taken in larger doses may have a constipating effect, due to absorption of irritant materials or to the mechanical effect of coating the gut over, as with a dusting-powder.

Experiment I.—Add a solution of 10 per cent. tannic acid to egg white, milk, and peptone solution.

Experiment II.—Hold 1 c.c. of the tannin solution in the mouth for a few minutes. What is the effect?

Experiment III.—Take a strip or ring of intestine of any animal and attach to a muscle lever and take tracing on a drum with the strip in normal saline. It is not necessary that it contract. Now replace the saline with 10 per cent. tannic acid or tincture of kino. Note the effect on the drum.

Experiment IV.—Test the action of one or more of the following solutions by gargling the throat with it:

a,	Tr. iodin	1
	Borax	1
	Aq. camphor	100
b.	Hydrochloric acid dilute	4
	Potassium chlorate	4
	Glycerin	15
	Water to	250
(*c*)	Alum	4
	Glycerin	5
	Water	100
(*d*)	Tincture ferric chloride	15
	Glycerin	15
	Water	100

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	Potassium chlorate	4
	Glycerin	15
	Water to	250
(*c*)	Alum	4
	Glycerin	8
	Water	100
(*d*)	Tincture ferric chloride	15
	Glycerin	15
	Water	100

ANTHELMINTICS.

(Anti, against; helminthos, worm.)

Anthelmintics are drugs used to remove intestinal worms. They are classified as:

1. Vermifuges, or drugs that expel the worm but do not kill it.
2. Vermicides, or drugs that kill the worm. The difference is more theoretical than practical.

An ideal anthelmintic would act on the worm and not be absorbed or injure the intestine. There are none such. All anthelmintics are absorbed to some extent and poisoning by them is not infrequent. Their use is possible because they are absorbed slowly. A cathartic is given before the administration to remove material that might protect the worm from the drug, and a cathartic is given after the drug for two reasons:

1. To aid in expelling the worm.
2. To expel and prevent absorption of the drug.

Oils are not recommended as cathartics in this case, because they dissolve most anthelmintics and aid their absorption. The most important anthelmintics are:

1. Thymol or oil of chenopodium for hookworm.
2. Oleoresin aspidii or pelletierin tannate for tape-worm.
3. Santonin or oil of chenopodium for round-worm.

If we had an ideal anthelmintic its action would be the same in the intestine as the following experiments in a test-tube. The difference, however, in the following experiments and the action *in vivo* is, that in the test-tube there is no absorption, while in the intestine absorption complicates the action.

Experiment I.—Demonstration; ascaris may be obtained from pigs at the slaughter house. Keep in NaCl and 0.1 per cent. sodium carbonate. For comparison place in beakers and keep at 37° to 40° C.

1. Normal.
2. Oil of chenopodium to saturation.
3. Thymol to saturation.
4. Male fern, 1 per cent. mixture.

Experiment II.—Tape-worms; the intestines of dogs usually contain worms of this type. Repeat Experiment I.

Experiment III.—Repeat Experiment I, using ordinary earthworms.[1]

[1] See Jour. Am. Med. Assn., 1919, lxxii, 1228; also Jour. Phar. and Exp. Therap., 1918, xii, 129.

SECRETIONS—MOVEMENTS—ANTISEPSIS.

1. Secretions.
2. Movements.
   Absorption.
   Excretion.
   Peristalsis.
3. Antisepsis.

Of these the secretions have been studied.

MOVEMENTS.

Absorption.—All parts of the tract absorb to some extent, but the small intestine and rectum seem to absorb drugs much more rapidly than the other parts. The stomach is practically not an absorbing organ. The following is the approximate time in which a large dose of strychnin, 0.1 gram, caused convulsions in a rabbit when administered in the same way in isolate loops or parts of the alimentary tract:

1. From rectum, convulsions in about two hours seven minutes.
2. Small intestine, convulsions in about two hours ten minutes.
3. Colon, convulsions in about two hours fifteen minutes.
4. From esophagus, convulsions in about one hour.
5. From stomach, no convulsions after two hours.

Most other drugs and water are not absorbed from the stomach; however, volatile drugs like alcohol are absorbed and facilitate the absorption of those drugs that are not absorbed.

Acceleration of Absorption.—Alcohol, carbon dioxide, volatile oils, spices and anything that will cause slight irritation of the gastric intestinal tract will aid absorption. If the irritation be too great it may have the opposite effect.

Retardation of Absorption.—There are a certain number of drugs that retard absorption and movement of the intestine. The most important are:

Morphin.
Atropin.
Tannins.
Bismuth salts.
Iron salts.
Calcium salts.
Colloidal material like gums, starches, pectins, etc.

Study the mechanism of the action in each case.

Excretion of Drugs into the Intestine.—Excretion into the intestine has been mentioned under intestinal secretions. Just how much occurs through the glands and by other channels is impossible to state. Most drugs that enter the body may, to some extent, be excreted into the intestine, either as such or as their oxidized or conjugated products. This is especially true of the heavy metals, alkaloids, drastic cathartics, arsenic, antimony, calcium salts and toxins.

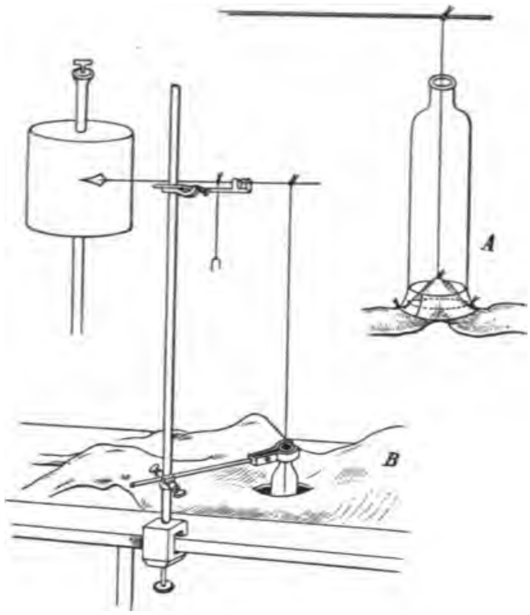


FIG. 17.—Trendelenburg method of recording intestinal contractions. *A*, tube attached to intestine; *B*, in position to take record.

Intestinal Movements.—There are three classes of movement seen in the intestine:

1. Pendulum movements due to contraction of the longitudinal muscles mainly.

2. Peristalsis, or an orderly forward progression of the intestinal contents, due to contraction of the circular muscles.

3. A rolling movement, described by Meltzer, Cannon and others, which consists of vigorous sudden waves of contraction which forces the intestinal contents forward through long segments of the small intestine.

Mechanism of the Movements.—The intestinal movements are automatic or myogenic in origin and not dependent upon the

nervous mechanism, but the orderly control of these depends on the extrinsic nerves. According to Meltzer, the rolling movement is due to a simultaneous augmentation of the vagus tone and a weakening of the sympathetic.

The Increase of Intestinal Movement.—Various agents may increase intestinal movements.

1. Shutting off the circulation by causing partial asphyxiation.
2. Mechanical stimulation, like pinching the gut wall, or increasing the intestinal contents with indigestible food, liquid paraffin, etc.
3. Chemical stimulation.
   (*a*) Gases:
      CO_2, CH_4, H_2S, etc.
   (*b*) Cathartics:
      Salines.
      Mercurials.
      Phenolphthalein, etc.
      Oils.
      Anthracenes.
      Colloids.
   (*c*) Pituitary extract.
      Barium salts.
      Glycerin suppositories.
      Nicotin.
      Eserin.

Retardation of Movement.—Most drugs that lessen intestinal secretion will also lessen intestinal movements. The most important are:

Opium derivatives.
Belladonna derivatives.
Tannic acid compounds.
Calcium salts.
Lead acetate.

INTESTINAL ANTISEPSIS.

In many cases it would seem to be a distinct gain if the intestinal tract could be disinfected. All attempts at this, however, has been disappointing; cathartics generally by flushing out the tract lessen putrefaction; but it is questionable whether the degree of change is sufficient to have any influence on the general condition of the body. Since infections generally are looked upon as detrimental because of the toxemia they produce, it would seem that in many cases gastro-intestinal derangement might be benefited by anything that rids the body of absorbable toxins.

CHAPTER IV.

ANTISEPTICS AND DISINFECTANTS.

THESE are general protoplasmic poisons.

Classification:

I. *General Disinfectants and Deodorizers.*—These may be:

1. Solids—for sinks, cesspools, water-closets, etc.
   - Copperas.
   - Ferrous sulphate.
   - Naphthalin.
   - Lime.
   - Chlorinated lime.
2. Liquids—for utensils of the sick room:
   - $HgCl_2$.
   - $ZnCl_2$.
   - Phenol.
   - Formaldehyde.
3. Gases—for disinfecting rooms and contents:
   - Formaldehyde.
   - Sulphur dioxide.
   - Chlorin.
   - Cresols in smoke.

II. *Disinfectants for Surgical Supplies:*

1. Heat, moist and dry.
2. Phenol, 5 per cent.
3. Alcohol, 70 per cent.
4. Formaldehyde.
5. Mercuric chloride.

The use of these agents should be demonstrated and the advantages and disadvantages of each considered.

III. *Genito-urinary Disinfectants:*

1. Hexamethylenamin.
2. Salicylates.
3. Benzoates.
4. Copaiba.
5. Oil of sandalwood.
6. Salol.
7. Creosote.
8. Boric acid.

Experiment I.—Different members of the class will collect a sample of urine for control, then take the average dose of the following drugs and repeat collection of urine every three hours:

1. Hexamethylenamin, 0.5 gm.
2. Sodium salicylate, 1.0 gm.
3. Sodium benzoate, 1.0 gm.
4. Copaiba, 1.0 c.c.
5. Oil of sandalwood, 0.5 c.c.
6. Salol, 1.0 c.c.
7. Creosote, 0.25 c.c.
8. Boric acid, 0.5 c.c.
9. Methylene blue (methylthionæ chloridium), 0.15 c.c.

Collect the urine in three, six and nine hours after the first dose; divide into three samples. One, leave as excreted; two, make slightly alkaline, and three, make slightly acid. Set all samples in an incubator or at room temperature and give estimate of the relative antiseptic value of each of the above. A sample of normal urine should be used as a control with each series.

IV. *Intestinal Antiseptics.*—In actual practice none of these are very efficient. They may lessen somewhat intestinal putrefaction.

Place 10 to 15 gm. of a very finely divided meat preparation mixed with ground pancreas, in large test-tubes; add the same amount (0.1 or 0.2 gm.) of each of the following drugs. Incubate at 40° C. Observe two or three times a day and estimate the relative efficiency from the odor:

1. Control.
2. HCl.
3. Calomel.
4. Charcoal.
5. Creosote carbonate.
6. Guaiacol.
7. Salol.
8. Tannin.
9. Thymol.
10. Bismuth subnitrate.
11. Glutol (gelatin formalin).
12. Hexamethylenamine.
13. Sodium salicylate.
14. Sodium benzoate.
15. B. Napthol.

V. *Antiseptic Dusting Powders.*—Place 15 c.c. of fresh defibrinated blood in a series of test-tubes; add to each of the series about 10

gm. of the following drugs. Close the tubes and incubate, observing every day. Notice the color:

1. Control.
2. Acetanilide.
3. Charcoal.
4. Kaolin.
5. Iodoform.
6. Glutol.
7. Talcum.
8. Bismuth subnitrate.
9. Zinc oxide.
10. Tannin.
11. Thymol diiodid (aristol).
12. Calcium carbonate.
13. Boric acid.
14. Betanaphthol.

Make a table of the results, putting the drugs in the order of their potency, dividing them into those which prevent putrefaction completely, almost entirely, those which delay, and those which have no action.

VI. *Drying or Absorbent Powders.*—Powders are frequently used as excipients when liquids are given in capsules, and it is necessary in such cases to select one that will absorb liquid. They are also used to absorb gases.

Mix 1 c.c. of defibrinated blood with 1 gm. of the powders mentioned in Experiment V in small dishes and observe and compare their consistence.

VII. *Antiseptic Action of Alcohol.*—Mix a cake of yeast with 100 c.c. of water. Add 10 gm. of dextrose and shake thoroughly. Compare the antiseptic action of alcohol at different strengths as follows. Fill a series of fermentation tubes as follows and place them in an incubator at 40° C. or at room temperature:

1. Equal parts of yeast, dextrose and water.
2. Equal parts of yeast, dextrose and 20 per cent. alcohol.
3. Equal parts of yeast, dextrose and 40 per cent. alcohol.
4. Equal parts of yeast, dextrose and 80 per cent. alcohol.
5. Equal parts of yeast, dextrose and 100 per cent. alcohol.
6. With yeast, dextrose 5 per cent. in alcohol 70 per cent.
7. With yeast, dextrose 5 per cent. in alcohol 90 per cent.

If facilities permit, different species of bacteria may be used instead of the yeast.

CHAPTER V.

DRUGS CHARACTERIZED BY THEIR ACTION CHIEFLY AFTER ABSORPTION.

The action of drugs after absorption may be exerted on one system or on a number of systems. As a rule, more than one system is acted upon. For this reason it is advisable to study the chief actions of the drug and then systematize these actions according to physiological or anatomical systems. It is also advisable to reverse the method of approach and to study the action of all drugs that act on a particular system, as the nervous system, heart, respiration or glandular system. It is not possible to use the two classifications satisfactorily in the same outline, so the work should be coördinated by using both classifications, *i. e.*, the total actions of one drug and a comparison of all drugs that affect each system. In the following outlines we have included most of the work on a simple drug under the system upon which the drug exerts its most important action. Caffein is found under drugs acting on the kidney and digitalis under the pharmacology of the heart. All the actions of alcohol may be studied; and the action of alcohol on the nervous system, heart, kidney, etc., should be compared with the action of all other drugs that act on these particular systems. Comparisons such as the action of aconite, digitalis, strychnin and epinephrin on the heart, or atropin, morphin and calcium on the intestine is both profitable and interesting.

DRUGS ACTING ON THE CEREBRUM.

I. The Alcohol Group.—The action of the alcohol group of drugs depends upon three chief points of attack.

1. The local irritant action—this is due to general action on the protoplasm. The antiseptic action, vomiting, gastric catarrh, degeneration of parenchymatous tissue, etc., are all due to the general protoplasmic action.

2. Food value—some of its uses in medicine depend upon the fact that it may be used as a food.

3. The action on the central nervous system—upon this depends the changes in reflexes, psychic changes, and anesthesia, with a consequent change in all other organs. The euphoria alcohol produces is due to an action on this system.

For an insight into the irritant action of alcohol, study Irritants, p. 65. Note carefully that much of the discussion of irritants or any other drugs are statements of facts, and some physical or chemical basis is often advanced as a possible explanation of the results which the changed physics or chemistry entail. No complete explanation can be given until we know more of the fundamental properties of living matter.

The irritant action of alcohol is due either to its direct action, or to the action of some of its oxidized products on protoplasm. The irritant action is manifested by redness, increased circulation, some local swelling or edema, probably pain, some change in function, manifested by vomiting, nephritis or the like.

Alcohol as a Food.—Study and carefully differentiate between drugs, poisons and foods. Foods are something that will give up energy to the body, repair waste and that will not injure the body. Unless it does all three things it need not be considered as a food. It may be a valuable drug without doing any of these things.

Outline for study of drugs acting on the nervous system:

I. Brain:
  Cerebrum:
    Psychic (drugs): stimulating—caffein, cocain, atropin, strychnin (?)—and depressing. The alcohol group: nitrous oxide, cannabis, morphin, hypnotics and depressants.
    Sensory (drugs): stimulating and depressing.
    Motor: stimulating and depressing. In general the same drugs affect each system in the same way.

By psychic functions we mean those higher qualities which have to do with attention, observation, judgment, perception, reflection, logical sequence and the like—those qualities mainly in the field of psychology. The dividing line between what is called psychic and what is considered as sensory is essentially indistinct—a kind of no man's land.

Sensation, or what belongs to the sensory part of the nervous system, cannot be sharply defined from the psychic, and sensations have not been satisfactorily classified by physiologists.

Formerly sensations were divided into

1. Special:
   - Sight.
   - Hearing.
   - Touch.
   - Taste.
   - Smell.
2. Common:
   - Touch.
   - Pressure.
   - Heat.
   - Cold.

A more recent classification is:

1. External or exterior senses:
   - Sight.
   - Hearing.
   - Taste.
   - Smell.
   - Pressure.
   - Temperature.
2. Internal or interior sensations:
   - Pain.
   - Muscle sense.
   - Hunger.
   - Thirst.
   - Appetite.
   - Sexual sense.
   - Fatigue.
   - The sensations of the semicircular canals.
   - The sensations from the visceral organs.

Motor.—The motor areas of the brain are located along the anterior surface of the fissure of Rolando. The pharmacology of the motor areas may be studied separately from the motor nerve endings or the reflex functions. The influence of drugs on the motor areas may be studied as follows:

Experiment I.—Anesthetize a dog and insert a tracheal cannula for artificial respiration. When the motor areas have been exposed place a cannula in the carotid for blood-pressure tracings.

To expose the motor areas: Fasten the animal belly down on the operating board. With a median incision cut the skin from the eyes to the occipital condyle. Detach as much of the temporal muscle from the bone as is necessary to expose the region of the

fissure of Rolando. This is well forward, and it is advisable to expose forward to the superciliary ridge. Feel the condyles of the lower jaw and join them with a line over the top of the head. Draw another line or thread between the outer canthi of the eyes. The fissure of Rolando lies a little posterior to the middle of the distance between these two lines. With a trephine, bore a hole a little to one side of the longitudinal sinus, which if injured will cause considerable trouble. Lay bare an adequate area of the brain so that the various motor areas may be stimulated with an electrode. In stimulating the motor areas, do not use a current that is highly unpleasant when applied to the tongue, keep the areas moist with saline, 0.8 per cent.

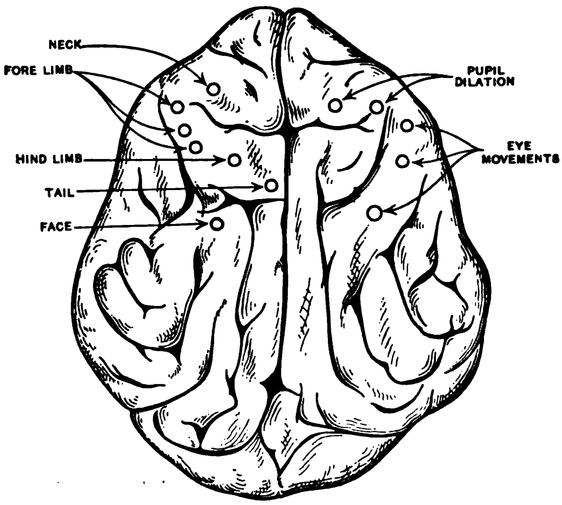


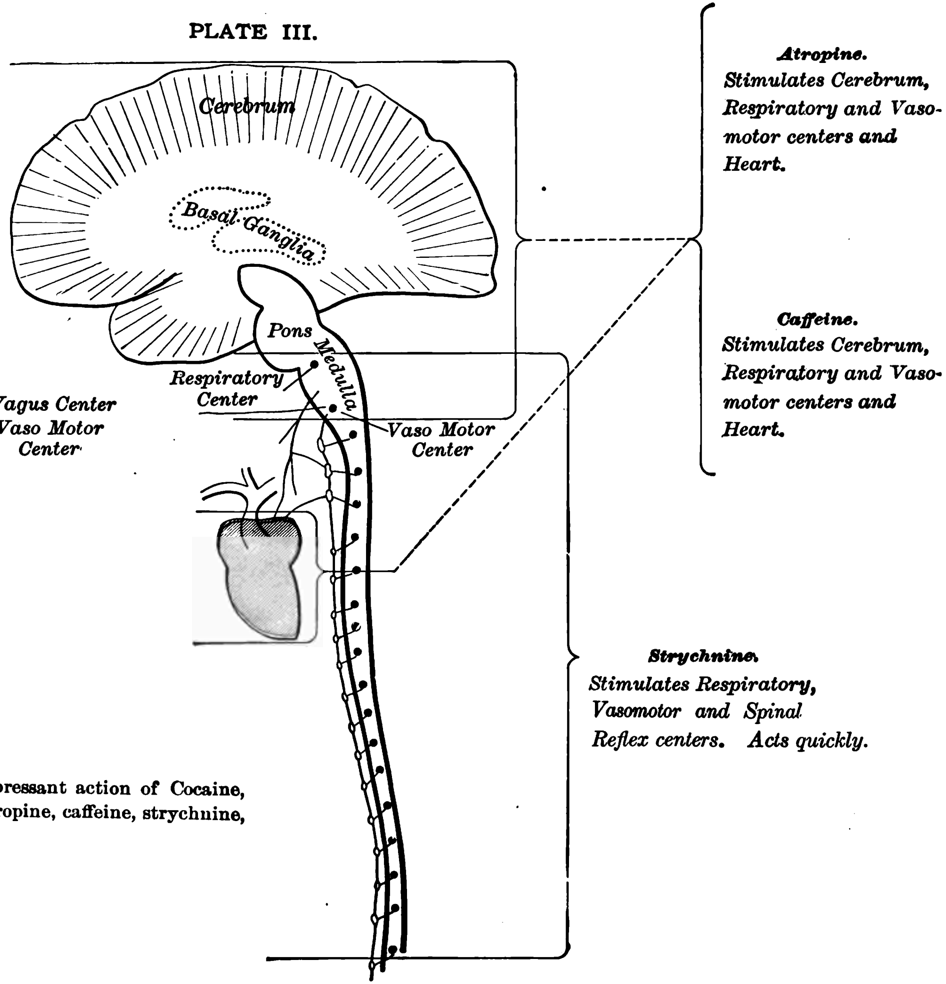
FIG. 18.—Motor areas in the dog's brain.

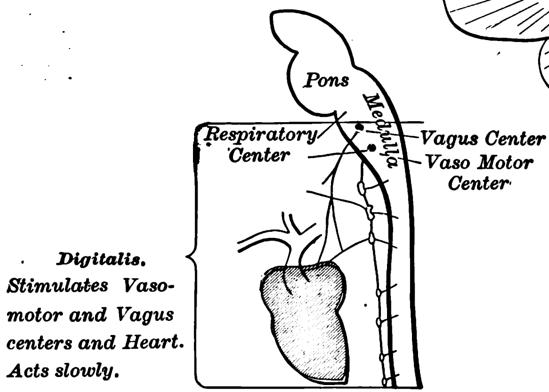
Ether is depressant to the motor areas, consequently if the anesthesia is too deep, no action can be obtained.

Experiment II.—Try the influence of light and deep anesthesia on the sensitivity of the motor areas. It is often necessary to remove the ether for some time before the areas can be located. Now deepen the anesthesia and repeat.

Experiments III.—Strychnin intravenously in amounts just leading to slight twitching will usually sensitize the mechanism of the motor areas. This sensitization is on the cord because direct application to the motor areas will not lead to such good results. Paint the areas with a little 0.01 per cent. strychnin and stimulate before

PLATE III.





The red color indicates a stimulant effect.

Compare with Plate V., showing the depressant action of Cocaine, which is shown here to be antagonized by atropine, caffeine, strychnine, and digitalis.

and after. Keep the strychnin from spreading or being absorbed. When satisfied as to the direct action of strychnin on the motor areas, inject intravenously 0.1 c.c. per kilo of 0.01 per cent. strychnin, and again stimulate the motor areas. Let the anesthetic be light at this period. Repeat the strychnin injection if necessary. When the motor area mechanism is decidedly stimulated, or when the animal commences to twitch, push the anesthetic until twitching ceases. In this way the action of any drug may be studied on the motor areas.

Cerebellum.—So little is known about the physiology of this part of the brain that there is practically no pharmacology. The cerebellum is concerned with the equilibrium of the body.

II. Medulla: Study the action of drugs on the various centers:

Respiration.
Vagus.
Vasomotor—constriction and dilation.
Salivary.
Emetic.
Sweat, etc.

III. Cord: The functions of the cord are mainly conduction and reflexes. Study and record the action of the various drugs on:

Sensation.
Motion.
Reflexes.

IV. Peripheral nerves:

Sensory and motor: study the action of drugs on the nerve trunk and endings; myoneural junction.

Drugs: Make a list of those that are stimulating and depressing to each of the above systems.

V. Autonomic:

Sympathetic system: this system has been discussed separately. Note that it is mainly motor. In the development of it from the central nervous system, only motor nerves wandered out. These may be constrictor or dilator in function. Study also the action of drugs on the nerve endings.

VI. Ganglion cells (drugs):

Depressing and stimulating.

Make an Outline of all Drugs Stimulating and Depressing the Various Parts of the Central Nervous System and Give Proofs that they Act in the Manner Indicated. Because they act on other systems also, these drugs cannot well be collected under one heading.

CHAPTER VI.

PHARMACOLOGY OF THE CRANIAL NERVES.

The following outline of the Pharmacology of the cranial nerves is given to indicate some things to watch for in the experiments, and as an aid to association.

I. The First Nerve: N. Olfactorius (L, Oleo, smell; facio, make). —Kant defined smell as taste at a distance. Taste and smell are closely related. The olfactory is a nerve of special sensation and hard to investigate because its receptive surfaces are intimately associated with those of the fifth nerve—a nerve of common sensation. For this reason true smells, or those substances which stimulate the olfactory only are hard to separate from pungent substances like vinegar which also stimulates the fifth nerve.

For the correlation of odor and structure we are indebted mainly to George Cohn (*Die Riechstoffe*, 1904) and Zwaardemaker (*Physiologie des Geruchs*, 1895).

Zwaardemaker separates pure odors into nine classes which have been arranged by Howell (*Text-book of Physiology*) as follows:

I. Odores ætherei or ethereal odors, such as are given by the fruits, which depend upon the presence of ethereal substances or esters.

II. Odores aromatici or aromatic odors, which are typified by camphor and citron, bitter almond and the resinous bodies. This class is divided into five subgroups.

III. Odores fragrantes, the fragrant or balsamic odors, comprising the various flower odors or perfumes. The class falls into three subgroups.

IV. Odores ambrosiaci, the ambrosial odors, typified by amber and musk. This odor is present in the flesh, blood, or excrement of some animals, being referable in the last instance to the bile.

V. Odores alliacei or garlic odors, such as are found in the onion, garlic, sulphur, selenium and tellurium compounds. They fall into three subgroups.

VI. Odores empyreumatici or the burning odors, the odors given by roasted coffee, baked bread, tobacco smoke, etc. The odors of benzol, phenol, and the products of dry distillation of wood come into this class.

VII. Odores hircini or goat odors. The odor of this animal arises from the caproic and caprylic acid contained in the sweat; cheese, sweat, spermatic and vaginal secretions give odors of similar quality.

VIII. Odores tetri or repulsive odors, such as are given by many of the narcotic plants and acanthus.

IX. Odores nauseosi or nauseating or fetid odors, such as are given by feces and certain plants and the products of putrefaction.

Beaunis[1] classified all substances which affect the olfactory mucous membranes into three groups, as follows:

1. Those which act only on the olfactory nerves:
   (a) Pure scents or perfumes, without pungency.
   (b) Odors with a certain pungency, *e. g.*, menthol.

2. Substances which act at the same time on olfactory nerves, and on nerves of common sensation (tactile nerves), *e. g.*, acetic acid.

3. Substances which act only on the nerves of common sensation (tactile nerves), *e. g.*, carbon dioxide.

Haller divided odors into:

1. Ambrosial or agreeable.
2. Fetid or disagreeable.
3. Mixed.

And in every-day life the division is usually made into:

1. Pleasant or agreeable.
2. Disgusting or disagreeable.

Chemistry and Physics of Odors.—It was formerly believed that in order that a substance be recognized as odoriferous, particles must reach the olfactory nerve through the air. However, odor may be detected when substances are dissolved in saline or in the pharmaceutic waters and taken into the nostrils.

The concentration of the substances in the liquid is of some importance, since cumarin, vanilin, oil of rose, etc., and other substances have different odors in strong and dilute solutions.

Practically, however, volatility is the most essential condition for production of an odor. Since volatility is mainly dependent on molecular weight, chemistry plays an important part. In chemical compounds it has been found that certain groups or radicles give rise to rather distinctive odors. These groups are called the osmophore groups (osme—odor; phero—to bear). Two or more osmophore groups may occur in the same substance. Investigation of

[1] Stewart: Text-book of Physiology.

these groups has not gone far enough to classify odoriferous bodies on their chemical groupings. The modifying influence of associated groups is not yet understood. Hydroxyl, aldehyde, ketone, nitrile, nitro and azoimide groups are all osmophoric, but may produce pleasant or unpleasant odors, and prediction as to the result is very uncertain.

However, certain facts are established:

1. Homologous derivatives usually have a similar odor.
2. Phenols have characteristic odors.
3. The odor of alcohols is usually pleasant.
4. Unsaturated substances, which are usually chemically reactive, generally have powerful odors. Triply linked compounds are usually unpleasant.
5. If an aldehyde has a pleasant odor, reduction alters the odor, but does not make it disagreeable.

Drugs that act centrally may stimulate or depress the sensation of the olfactory nerve, strychnin and caffein stimulate, chloral depresses. Cocain applied to the nasal mucous membranes paralyzes the sensation of smell entirely. Marked changes in the nerve may occur in disease and the sensation of smell may be entirely abolished (anosmia). Overstimulation may also cause this.

Fatigue of the nerve is quite common. Odors soon give no sensation when the stimulation is continued, and unpleasant odors such as coal gas, etc., by continued action soon lose their effect.

Experiment.—Select different volatile oils, phenols, etc., and dilute to get a pleasant odor. Let each group of students work with one odor. After smelling set to the side and cocainize the nose by plugging it with cotton dipped in 0.1 per cent. cocain in 1 to 1000 epinephrin, after a few minutes remove the cocainized cotton plug and determine whether or not, the sense of smell has been influenced.

II. The Second Nerve: N. Opticus.—The second cranial or optic nerve is the essential organ of vision. The layer of rods and cones are the receptive endings and transmit impulses to the ganglion cell layers through the bipolar cells. These bipolar cells may be regarded as similar in mechanism to the spinal ganglion cells, while the retinal ganglion-cell layer, is a part of the central nervous system. Drugs that act on the optic nerve are usually those that act on the central nervous system.

Drugs Acting on the Optic Nerve.—Methyl alcohol, especially when its use is continued, but even one dose may so injure the nerve as to cause permanent blindness. Buller and Wood collected 54 cases in the United States and Canada. In the month of December, 1911,

70 deaths from wood alcohol in cheap spirits occurred in the municipal lodging house in Berlin. Death, however, may occur without the optic nerve being directly involved. Quinin sometimes causes a derangement of vision, but not so often as it disturbs hearing. Filix mas, santonin, pellitierin, nicotin, alcohol, carbon bisulphide, napthols, etc., may also act on the optic nerve. These actions, however, are relatively rare. Strychnin and caffein sensitize the nerve while central depressants have the opposite effect.

For experiments see Autonomic Drugs and the various drugs mentioned.

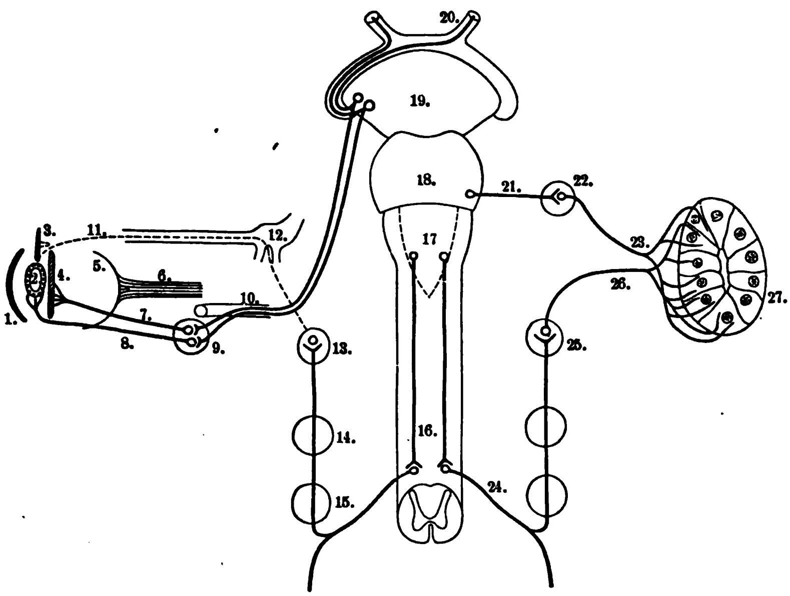


FIG. 19.—Diagram to show nerves of eye and submaxillary gland. *1*, cornea; *2*, sphincter pupillæ; *3*, dilator pupillæ; *4*, ciliary muscle; *5*, retina; *6*, optic nerve; *7*, *8*, short ciliary nerves; *9*, ciliary ganglion; *10*, third cranial nerve; *11*, long ciliary nerve; *12*, Gasserian ganglion; *13*, *25*, superior cervical ganglia; *14*, middle cervical ganglion; *15*, inferior cervical ganglion; *16*, motor nerve; *17*, medulla; *18*, cerebellum; *19*, cerebrum; *20*, optic nerve; *21*, seventh nerve; *22*, ganglion; *23*, chorda tympani; *24*, sympathetic nerve; *27*, submaxillary gland.

III. The Third Nerve: N. Oculomotorius.—The third nerve is a purely motor nerve that innervates both striated and non-striated muscle. The striated muscles, internal, superior and inferior rectus, and the inferior oblique. These nerves arise from the principal nucleus of the third nerve and go directly to the muscle. The third nerve also innervates the intrinsic muscles of the eyeball—the ciliary and the sphincter of the iris. The portion innervating the

sphincter arises from the Eppinger-Westphal nucleus, while those innervating the ciliary muscles arise from the median nucleus. Both these fibers pass to the ciliary ganglion before going to the muscles. They are therefore autonomic in structure. The pharmacology of the third nerve is concerned entirely with the autonomic portions of the nerve and is studied especially under the eserine, pilocarpin and atropin groups of drugs.

IV. The Fourth Nerve: N. Trochlearis.—The fourth nerve is a motor nerve supplying the superior oblique muscle of the eyeball. The pharmacology of all motor nerves to striated muscle is essentially the same. Curare and quaternary ammonium bases paralyze the endings while eserin stimulates them. Any drug may have an action on the fibers when applied directly to them, but no drug has an observable action when given any other way. The centers of the nerve may be stimulated by the general centrally acting stimulants or depressed by the central depressants.

V. Fifth Nerve: N. Trigeminus.—This is a mixed motor and sensory nerve. The motor fibers innervate the muscles of mastication—striated muscles. The pharmacology is concerned with the sensory part which mediates sensations of pressure, pain, and temperature to the face, scalp, eye, nose, portions of ear, mouth and tongue. It is a mediator of common sensations. Some few physiologists think it contains some nerves of special sensation that are given off through the seventh and ninth nerves.

The pharmacology is in general that of sensory nerve endings. Irritation of the fifth nerve endings by saponin or other irritating drugs, by dust, pressure through inflammation of the mucous membranes, etc., causes sneezing. A trace of aconite also, in the nose will cause sneezing, coughing, a flow of mucus and may produce vomiting. Cocain by depressing the endings prevents this. Drugs that act centrally may stimulate or depress the fifth nerve centrally.

VI. Sixth Nerve: N. Abducens.—The sixth nerve is a purely motor nerve. It innervates the external rectus. Its pharmacology is the same as that of any other motor nerve.

VII. Seventh Nerve: N. Facialis.—This is mainly a motor nerve but it carries some sensory fibers. The motor fibers go to muscles and glands. The muscular fibers go to the muscles of the face, scalp and ear. The pharmacology of these is mainly the pharmacology of voluntary motor fibers.

The glandular branches are much more important. They are carried to the glands in the chorda tympani. The pharmacology of the chorda tympani is studied under the atropin and pilocarpin

group of drugs. Pilocarpin and eserin stimulate the nerve endings, while the atropin paralyzes them.

VIII. The Eighth Nerve: N. Acousticus.—This is a special nerve and there is but little pharmacology known. Certain drugs like quinin, salicylates, etc., often produce ringing in the ears, but whether this is due to a direct action on the nerve or due to changes in the circulation of the region is not known. Strychnin and caffein increase the acuteness of hearing by a central action. Morphin, chloral, bromides, etc., depress by a similar mechanism.

Experiment. (Optional).—Place the ear to a fixed opening in the wall or instrument provided and determine accurately the distance which each student can hear the ticking of a watch. Now give,

0.03 gram morphin, or
1.00 gram chloral, or
1.00 gram potassium iodide, or
1.50 c.c. tincture cannabis, or a dose of any hypnotic, and determine the change in hearing after one or two hours.

Similarly with other students the change produced by:

$\frac{1}{30}$ grain strychnin,
2 grains caffein, or
20 c.c. 80 per cent. alcohol.

IX. The Ninth Nerve: N. Glossopharyngeus.—This is a mixed nerve. It supplies motor nerves to the pharynx and base of the tongue. The pharmacology of these is the same as other motor nerves. It also supplies secretory fibers to the parotid gland, through Jacobson's nerve. This has the same pharmacological reactions as the chorda tympani.

The sensory nerves supply the posterior third of the tongue, and the mucous membrane of the back of the mouth. These parts are influenced in the usual way by aconite, by cocain, etc.

It also supplies taste nerves to the posterior third of the tongue but these reach it from the fifth nerve, while fibers of the fifth nerve —lingual—supplies the tip. Some physiologists believe that the ninth nerve alone is the nerve of taste.

Before a substance can stimulate taste it must be soluble in the fluids of the mouth. Accordingly as they affect the taste, sapid substances have been classified as follows:

1. Sweet.
2. Bitter.
3. Acid.
4. Saline.

Regarding the mechanism by which sapid substances stimulate

the gustatory nerve endings we know but little, but the stimulus acts on the end-organs and not on the nerve trunks. Nerve trunks in general are not stimulated by any pharmacological agent, unless it be applied directly; but a sensation of taste is not developed by direct application to the nerve trunk. Attempts have been made to find a chemical group responsible for taste, but little progress has yet been made. Acids and bases owe their characteristic tastes to the H and alkalies to OH ions.

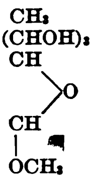
Sternberg ascribes the bitter taste of alkaloids to their cyclic constitution. In the Mendelejeff periodic classification of the elements, the sweet-tasting elements boron, aluminum, scandium, yttrium, lanthanum are found in the third group, while lead and cereum are in the fourth. Beryllium another sweet-tasting element is in the second, while chlorin, which often gives rise to sweet compounds, is in the seventh.

The bitter elements—magnesium, zinc, cadmium and mercury—are found in the second. Sulphur in the sixth group often gives rise to bitter compounds.

The hydroxyl group has often been associated with a sweet taste. Sternberg (Geschmack and Geruch) has pointed out that in organic compounds, in order to have a sweet taste, the alkyl groups must not exceed the OH groups by more than one or their combination will be bitter. Thus rhamnose:

$$CH_3(CHOH)_4CHO$$

is sweet, but methyl rhamnose



is bitter.

Again, the sweetness in an homologous series increases with the increase of hydroxyl groups, *e. g.*, glycocol:

$$\begin{array}{l} CH_2OH \\ CH_2OH \end{array}$$

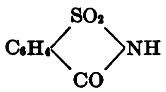
is sweet, but not so sweet as glycerin:

$$\begin{array}{l} CH_2OH \\ CHOH \\ CH_2OH \end{array}$$

And glucose:

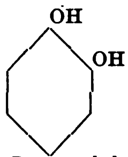
$$\begin{array}{l} CH_3 \\ (CHOH)_4 \\ CHO \end{array}$$

is still sweeter. That other factors than the OH groups enter into the production of a sweet taste is shown by the fact that lead acetate is sweet, yet contains no OH groups, and saccharin

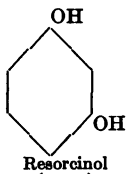


is three hundred times sweeter than sugar and contains no OH groups. It has been suggested that the stimulation of the taste buds is a physical process due to intramolecular vibrations, but we have no way of testing such a suggestion.

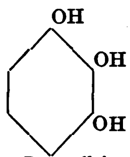
Again in those aromatic bodies containing an OH group, the position of this in the ring and the relation to other groups is interesting, *e. g.*:



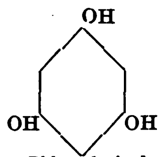
Pyrocatechol (bitter)



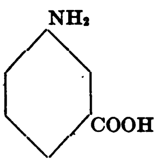
Resorcinol (sweet)



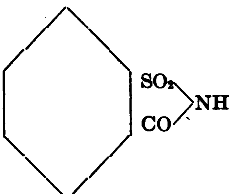
Pyrogallol (bitter)



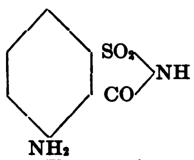
Phloroglucinol (sweet)



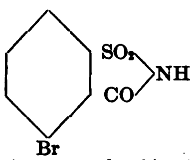
Anthranilic acid (sweet)



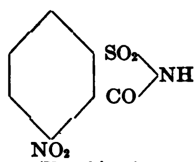
Saccharin (very sweet)



(Very sweet)



(First sweet, then bitter)



(Very bitter)

This shows that the arrangement of the molecule is of considerable importance. This is further illustrated by the differences in the taste of optical isomers: dextro-asparagin is sweet while levo-asparagin is not, and dextroglutaminic acid is sweet whereas the levo acid is tasteless.

In a recent study of the chemistry of taste, Oertly and Meyers[1]

[1] Jour. Am. Chem. Soc., 1919, xli, p. 855.

have worked out a theory relating to the aliphatic sweet stuffs. They think that taste is dependent on two factors—a glucophoric and an auxogluc. They define a glucophore as a group of atoms which has the power to form sweet compounds by uniting with a number of otherwise tasteless atoms or radicals. An auxogluc is defined as an atom or radical which combined with any of the glucophores yields a sweet compound.

The following radicals are found to be glucophores in the sense of their theory:

$-CO-CHOH-(+H)$,	$CH_2OH \cdot CHOH-$,
$CO_2H \cdot CHNH_2-$,	CH_2ONO_2-
$C^{H_2-x-}_{Hl_x}$	$C^{H_3-x}_{Hl_x} \cdot C^{H_2-y-}_{Hl_y}$

Some others may very likely be included later on.

The following atoms or radicals seem to act as auxoglucs, yielding with glucophores sweet compounds:

(*a*) H, hydrogen.

(*b*) The radicals $C_nH_{2n}+1^\circ$ of saturated hydrocarbons, containing from one to three carbon atoms. Example, CH_3CH_2.

(*c*) The radicals $C_nH_{2n}+1^\circ$ of monohydric alcohols, n being equal to one or two. Example, CH_2OH.

(*d*) The radicals $C_nH_{2n}-1^\circ{}_n$ of polyhydric alcohols. Example, $CH_2OHCHOH$.

Experiment.—Samples of the various drugs may be tested to determine the accuracy of the above statements.

X. The Tenth Nerve: N. Vagus.—The vagus is a mixed nerve, with a wider distribution than any other nerve in the body. It sends sensory nerves to the mucous membranes of the larynx, trachea, lungs, esophagus, stomach, intestines, gall-bladder and ducts. It sends motor fibers to some small intrinsic striated muscles of the larynx and unstriated muscles of the heart, lungs and intestine. From the pharmacological standpoint these last are the most important, and from this point of view it is mainly an autonomic nerve and the most important of the autonomic nerves.

The action of drugs on the vagus endings has been studied under autonomic drugs, atropin and pilocarpin, the glands, the heart and intestines.

Nicotin first stimulates and then paralyzes the ganglia on the vagus.

The vagus center is stimulated by strychnin, picrotoxin, digitalis, epinephrin, atropin, by asphyxia and high blood-pressure. The

center is depressed by morphin, the alcohol-chloral groups, bromides, etc. See experiments under Heart, Autonomic Drugs, etc.

XI. The Eleventh Nerve: N. Acessorius.—This is a motor nerve supplying the sternomastoid and trapezius muscles.

XII. The Twelfth Nerve; N. Hypoglossus.—The twelfth nerve is a motor nerve supplying the muscles of the tongue, the extrinsic muscles of the larynx and hyoid bone.

The pharmacology of these nerves is unimportant, and if involved could be influenced only in a manner similar to other voluntary nerves. The centers would be stimulated by strychnin, caffein, etc., and depressed by morphin and the alcohol-chloral group.

CHAPTER VII.

PHARMACOLOGY OF THE HEART AND BLOOD-PRESSURE.

FACTORS concerned in the maintenance of blood-pressure:

1. The amount and the condition of the fluid in the circulatory system. The amount is about one-thirteenth of the body weight.

2. The viscosity of the blood, or rather its colloidal condition, has an important part to play. It is well known that injected saline will not sustain the pressure as well as 6 per cent. gum acacia or other colloidal solution. Even homogeneous blood beyond a definite volume will not remain in the bloodvessels any length of time. Magnus found that 20 to 50 per cent. of the volume of such injections left the vessels and was expressed into the tissues within three to five minutes after the infusion.

3. The peripheral resistance—due to size of vessels and condition of muscle tone.

4. The condition of the heart itself.

A certain blood-pressure seems necessary for the life and functioning of protoplasm. This is vividly manifested in the kidney which stops secreting when the pressure reaches 40 mm. of mercury.

In experimental work the condition of the fluid, as to volume amount and to some extent its viscosity, can be varied at will and the effect studied. The peripheral resistance can also be modified mechanically and by the action of drugs. Drugs which increase the tone of the muscles either directly or indirectly will tend to increase blood-pressure. Drugs like nicotin, epinephrin and digitalis that constrict the vessels will raise the pressure, while nitrites, peptones, etc., that dilate the vessels will lower the pressure.

The following drugs stimulate the heart either directly or through the nerves, and therefore tend to raise the blood-pressure:

Caffein.
Strychnin.
Atropin.
Cocain.
Nicotin.
Epinephrin.
Pituitrin.
Ca, Ba, Pb, and other heavy metals.

Heart depressants, which directly or indirectly weaken the heart muscle, reduce the tone of the muscle and lower the blood-pressure:

Aconite.

The alcohol group.

Nitrites.

Study the mechanism of the action of these on the heart and vessels under these various drugs.

BLOOD-PRESSURE.

The action of drugs on the blood-pressure is so important that the following summary of the main causes affecting the blood-pressure are given.

Blood-pressure may be lowered by:

I. Slow action of the heart. This may be due to:

A. Stimulation of the vagus center, fibers, or endings in the heart.

(*a*) Directly by the action of a drug.

(*b*) Indirectly by increased blood-pressure.

(*c*) Indirectly by increase in the carbon dioxide content of the blood.

(*d*) Reflexly by stimulation of any sensory nerve.

II. Increased excitability of the vagus endings in the heart.

(*a*) By drugs.

(*b*) By toxins.

(*c*) By changes in the function of ductless glands.

(*d*) Indigestion, products of.

III. Paralysis of sympathetic neurons—roots, fibers or endings.

IV. Weakness of the heart muscle from any cause.

B. Smallness of the amount of blood sent out at each systole; due to

(*a*) Hemorrhage.

(*b*) Shock.

(*c*) Contraction or obstruction of pulmonary vessels.

(*d*) Great dilation of the venous system.

(*e*) Decompensated heart.

C. Dilation of the small arteries. This would be difficult to disassociate from dilation of the capillaries. It would occur

(*a*) By paralysis of the vasoconstrictor center.

(*b*) By paralysis of the arterial walls.

Both of these may be due to the action of drugs or toxins directly, or reflexly through the depressor nerve, division of the cord or section of the splanchnics, ablation of the brain or great depression of the brain by opiates or narcotics.

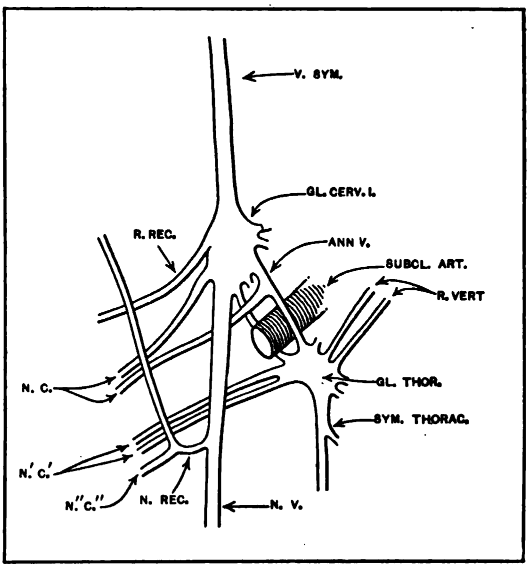


Fig. 20.—Diagram of last cervical and first thoracic ganglia in the dog. (After Foster.)

Blood-pressure may be increased by:

A. By quick action of the heart:

(*a*) By paralysis of any part of the vagus mechanism.

(*b*) Stimulation of the sympathetics.

Either of these conditions may be caused directly by drugs. Atropin will paralyze the vagus. Epinephrin will stimulate the sympathetics. Nicotin will first stimulate, later paralyze all ganglion cells.

B. (*a*) By the heart expelling a larger amount of blood at each beat, as after the administration of digitalis.

(*b*) Hypertrophied heart.

(*c*) Increased tone of the heart muscle.

C. By contraction of the small arterioles and capillaries:

(*a*) By irritation of the vasoconstrictor center.

1. Directly by drugs or toxins.
2. Indirectly by carbon dioxide accumulation in the blood.

3. Reflexly through the cervical sympathetic.
4. Reflexly through other nerves, *e. g.*, the vagus in non-anesthetized animals.
5. Reflexly through any sensory nerves.

(*b*) Direct stimulation of the vascular walls.

1. By drugs.
2. In operations where the peripheral ends of vasoconstrictor nerves are stimulated.

D. By conditions which increase the tone of the skeletal muscles.

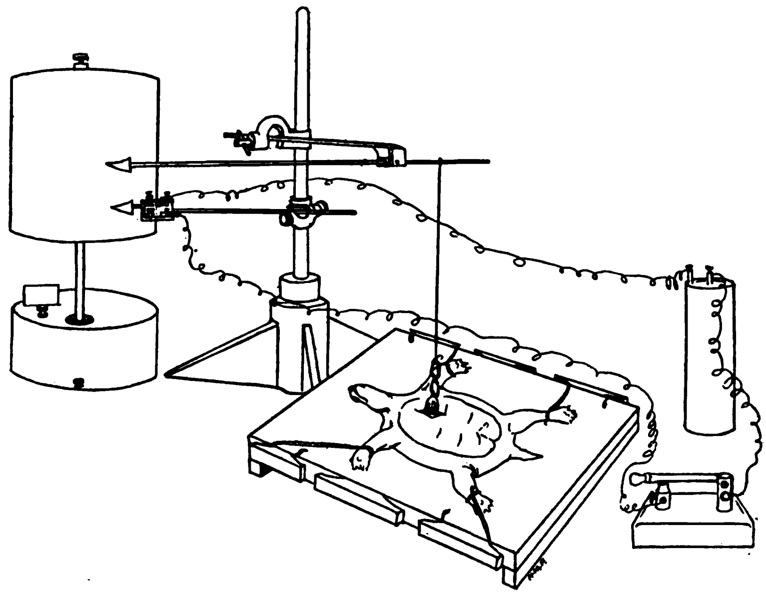


FIG. 21.—Suspension method of recording heart contractions.

DIGITALOID DRUGS AND DIGITALIS.

The main actions of the digitaloid drugs are:

1. A specific stimulating action on the heart which renders it more irritable, with a tendency to more rapid action.

2. Stimulation of the vagus center which tends to slow the heart.

3. Stimulation of the vasoconstrictor center.

4. Direct stimulation of the musculature of the vessels particularly strong in the splanchnic region, with a tendency to lessen the secretion of urine.

5. An irritant action on the stomach or wherever applied; this causes vomiting when taken into the stomach in large quantities and pain when applied to mucous membrane.

6. A direct stimulating action on the vomiting center. (Hatcher.)
7. A tonic action on the central nervous system.
8. A tonic action on endothelial and lymphatic tissues.
9. A marked diuretic action in cases of edema through changes in the circulation.

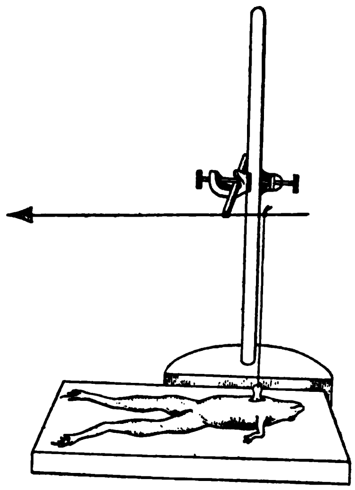


FIG. 22.—Suspension method of recording heart tracings.[1]

Experiment I.—*Action on the Frog or Turtle Heart:* Isolate the vagus; take a tracing of the normal heart by the suspension method. Stimulate the vagus. Apply a few drops of an infusion of digitalis to the exposed heart. This may be repeated every five minutes until the heart stops in ventricular systole. Study the action of the vagus every ten minutes and record its effect at the different stages of digitalis action.

Experiment II.—Prepare several turtle heart strips and take tracings in the usual way. When the strips beating are regularly place:

1. In a bath of 0.002 per cent. digitalis in saline.
2. In a bath of 0.005 per cent. digitalis in saline.
3. In a bath of 0.01 per cent. digitalis in saline.

Compare results.

Experiment III.—Place a cannula in the vena cava of a frog (Figs. 23 and 24), or turtle and perfuse with 0.001 per cent. digitalis in Ringer's solution. What is the effect on the heart beat? Take tracing.

Experiment IV.—*Action of Digitalis on the Heart and Respiration of a Dog.*—1. Weigh animal and record pulse and respiration-rate, general appearance and condition.

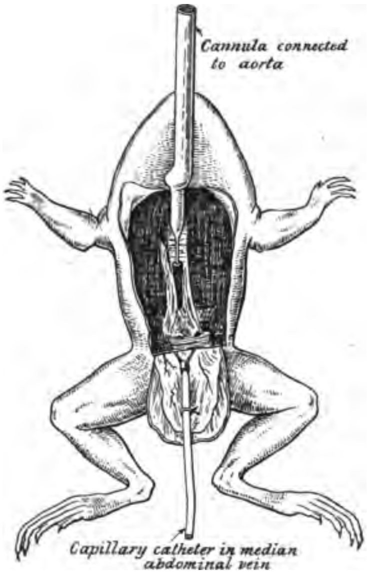


Fig. 23.—Frog-perfusion method, to study action of drugs on vessels. (Fuehner.)

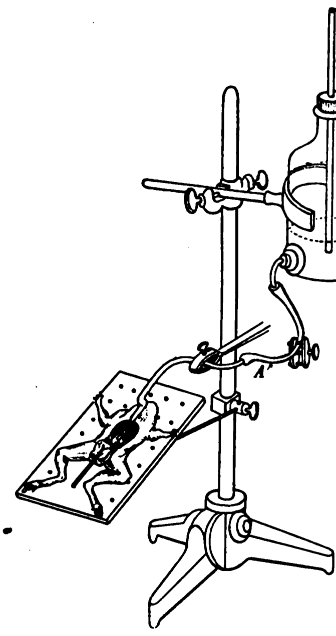


Fig. 24.—Fuehner apparatus arranged for perfusion.

2. Inject slowly into the femoral vein 0.4 c.c. per kilogram of 1 per cent. infusion of digitalis without anesthesia.

3. Record observations as in 1 every five minutes.

Experiment V.—*Action of Digitalis on the Heart and Respiration.*—1. Record weight, heart-rate and respiration of a dog.

2. Anesthetize in the usual way; isolate one vagus nerve; ligate cut and prepare peripheral and central ends for stimulation.

3. Arrange for blood-pressure and respiration tracings.

4. Take normal tracings and show the influence of vagus stimulation, central and peripheral. Also similar stimulation of the sciatic.

5. Slowly inject into the femoral vein 0.2 c.c. of 1 per cent. infusion of digitalis per kilogram.

6. Stimulate vagus and sciatic as in 4.

7. Repeat 5.

8. Stimulate vagus and sciatic as in 4.

9. Repeat 5 if thought advisable.

Experiment VI.—*Demonstration; Myocardiagram and Blood-pressure under Digitalis.*—1. Anesthetize a dog with ether. Prepare for blood-pressure and myocardiagraph tracings; superimpose the tracings.

2. Inject slowly 0.4 c.c. of 1 per cent. infusion of digitalis per kilogram of body weight into the femoral vein and take continuous tracing. In thirty minutes repeat the dose if necessary.

Experiment VII.—*Digitalis as a Diuretic.*—1. Weigh and anesthetize a dog. Prepare for blood-pressure tracing. Insert a catheter into the bladder and measure secretion of urine in drops for thirty minutes.

2. Inject 0.5 c.c. of 1 per cent. infusion of digitalis into the femoral vein every five minutes for four or five times or until the animal gets about, 0.4 c.c. per kilo. Note the effect on the urine for thirty minutes.

3. Inject 1 c.c. per kilo of 2 per cent. theobromin sodium salicylate and compare the urine secretion with that of digitalis for thirty minutes.

Experiment VIII.—*Standardization of Digitalis. Digitalis; Strophanthus; Squill.*—For the physiological standardization of this series the "one-hour frog" method is recommended. The method consists in ascertaining the dose of the drug or preparation that will bring the heart of a frog weighing 15 to 25 grams to systolic standstill in one hour. All measurements in the operation should be carried out with the same degree of accuracy used in quantitative chemical estimations.

Frog: Use healthy specimens weighing between 15 and 25 grams.

Storage: The animals should be kept in a cool room, preferably where the temperature does not rise above 15° C. The bottom of the tanks should be covered with running water, or, if this is not convenient, the water in the tank should be changed four times daily.

An hour before the animals are used they should be kept in the laboratory in order to get acclimated to temperature. Weigh within 1 gram.

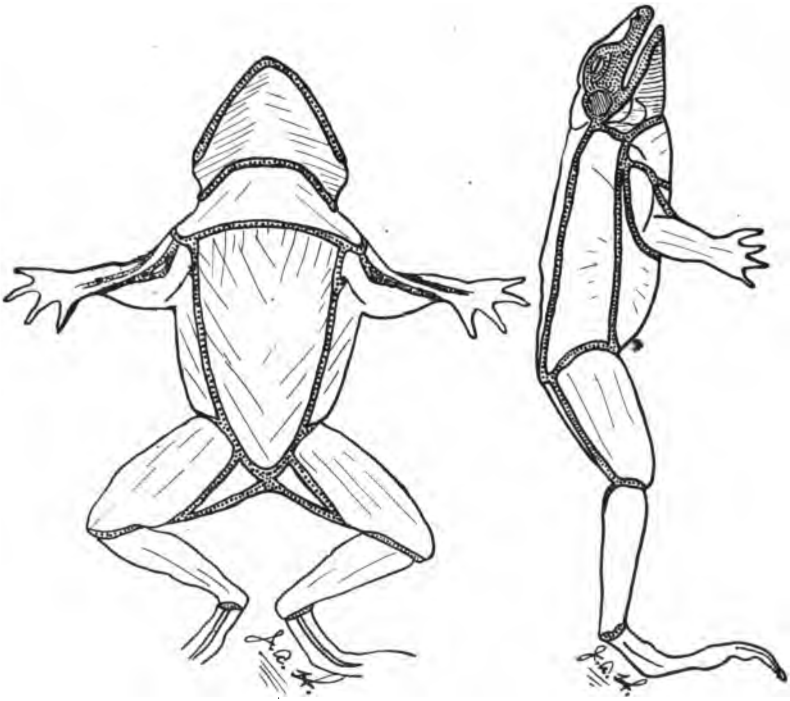


FIG. 25.—Figures showing the lymph sacs of the frog as seen from the ventral surface. Lymph sacs as seen from the side. For pharmacological purposes these sacs need not be named. (After Ecker.)

Dosage: Never inject more than 0.015 c.c. for each gram of frog. A larger volume than this is injurious from the volume alone. No attention need be paid to the alcoholic content unless this is over 20 per cent. of the injected material. In such cases evaporate the alcohol on a water-bath and dilute or make up volume with 0.07 per cent. sodium chloride: if there is a cloudiness or a precipitate, shake the solution before injecting. Injections should be made through the floor of the mouth into the anterior lymph sac

with a hypodermic. Do not puncture the skin, because there may be a leakage. Since the dose of a standard preparation of digitalis tincture is 0.006 c.c. per gram weight of frog, the first trial should vary from 0.004 c.c. to 0.008 c.c. per gram. At the end of an hour the frogs should be pithed, both brain and cord, and the heart examined. For the correct end-reaction the ventricle is stopped in systole and the auricles dilated. If these are stimulated there may be feeble contraction, but no general contractions is allowed. After this preliminary trial one knows approximately what the standard dose is; for instance, it may be between 0.005 and 0.006 or between 0.006 and 0.007. Another trial, working with dilutions between these figures, will determine the dosage accurately. The U. S. P. adopts the following as standard doses:

	Gram or milliliter for each gram of body weight of frog.
Standard dose of ouabain	0.0000005
Digitalis: Leaves (in the form of tincture)	0.0006
Fluidextract	0.0006
Tincture	0.006
Strophanthus: Seed (in the form of tincture)	0.000006
Tincture	0.00006
Squill: Dried squill (in the form of tincture)	0.0006
Fluidextract	0.0006
Tincture	0.006

Experiment IX.—*Hatcher's Cat Method of Standardizing Digitalis.*—One milligram of crystallin ouabain or 100 mg. of digitalis per kilogram of body weight when introduced slowly intravenously will kill a cat in about an hour. Not less than an hour should elapse in the injection or the method is not advised. Hatcher recommends the following procedure:

Anesthetize an animal with ether and place a cannula into the femoral vein for injection from a burette. The preparation to be injected is diluted with normal salt solution to such a strength that roughly 10 c.c. of the dilution per kilogram are required to cause death under the conditions of the experiment (1 c.c. of tincture plus 9 c.c. of normal saline). The injection is made slowly and continuously into the femoral vein of the cat at such a rate that 1 per cent. of the fatal dose is injected in a minute of time until toxic symptoms develop, when the injection is interrupted for ten minutes. If death does not occur the injection is resumed at the same rate as before and continued until the symptoms show the approach of death. If preferred, about half of the fatal dose may be injected within a period of fifteen minutes, after which the injection is interrupted for ten minutes and then continued at the rate of about 1

per cent. of the estimated fatal dose per minute until the appearance of toxic symptoms, when the injection is interrupted, as already mentioned.

Experiment X.—*The Gold Fish Method of Pittinger and Van der Kleed.*—Demonstration: Pittinger and Van der Kleed[1] have advocated the use of gold fish instead of frogs as a method of standardization of digitalis. The method has never been completely developed. The advantages claimed were simplicity and cheapness, but the latter does not hold now. The size of the fish is unimportant because the absorbing surface of the gills corresponds in all sizes. The following protocol taken at 27.5° C. will illustrate the method. The best temperature to employ still remains to be determined. In the following experiment eight fish were placed in beakers, each containing the same strength of solution in order to determine the individual variation in susceptibility to digitalis.

Dilution of fluidextract.	Weight of fish, grams.	Temperature.	Time required to cause death. Minutes
1 to 1000	34.1	27.5°	58
1 to 1000	27.9	27.5°	52
1 to 1000	5.5	27.5°	59
1 to 1000	5.0	27.5°	47
1 to 1000	2.3	27.5°	54
1 to 1000	3.1	27.5°	55

Experiment XI.—Students should divide in groups and group:

1. Take 1 c.c. tincture of digitalis every four hours for six times.
2. Take 2 c.c. tincture of digitalis every four hours for six times.
3. Take 3 c.c. tincture of digitalis every four hours for three times.
4. Take 4 c.c. tincture of digitalis in one dose.

Record pulse, respiration and general condition for forty-eight hours.

STANDARDIZATION OF SUPRARENAL GLAND.

This method depends on the experimental findings that 1 gram of dried suprarenal gland will raise the blood-pressure of a dog to the same degree as 10 mg. of levo-methyl-amino-ethanol-catechol.

Standard Solution.—1. Prepare an aqueous solution of levo-methyl-amino-ethanol-catechol (1 to 1000), using enough dilute hydrochloric acid to get a clear solution. From this solution prepare a solution of 1 to 100,000 by diluting 1 c.c. up to 100 with 0.9 per cent. sodium chloride.

2. Weigh out 1 gram of finely divided powder of suprarenal gland. Macerate twenty-four hours in 100 c.c. of distilled water, containing

[1] Jour. Am. Pharm. Assn., 1915, p. 427.

10 c.c. dilute hydrochloric acid (10 per cent.), shaking frequently. Filter through a dry filter.

Dogs.—Use a medium-size animal. Anesthetize with ether. Insert cannula in carotid for blood-pressure estimation. Insert cannulæ in each femoral vein and connect with a burette with a rubber, so that injections may be made. Injections should be made with glass syringes graduated to 0.05 c.c. The animal should be kept deeply anesthetized, and if there is any twitching sufficient curare should be injected to prevent this. Usually this is not needed. Take blood-pressure on a long kymograph.

Inject 1 c.c. of the standard solution and wash in with saline. Note the height of the pressure. After five minutes inject 1 c.c. of the gland or solution to be tested. Wait five minutes between each injection and change the dose of one or the other solutions until the blood-pressure rise is the same. In this way the strength of the unknown, in terms of the standard, may be ascertained.

ACONITIN.

The active principle of aconite is aconitin.

Aconitin is an alkaloid, peculiar from the fact that it stimulates sensory nerve-endings—those of common sensation, even when it is given systemically. The only other drug that does this is veratrin. It has a similar action if applied locally.

The main actions of aconitin are:

1. A prickling, tingling sensation due to an action on the terminal sensory nerves. Large doses may cause paralysis of these endings.
2. Depression of the heart due to central vagus stimulation—maybe followed by paralysis.
3. Stimulation and paralysis of all medullary centers.
4. A complicated action on the heart.

(*a*) There may be acceleration due to nausea and to gastric irritation.

(*b*) Slowing due to stimulation of the vagus center.

(*c*) Quicker heart from direct action, and fatigue of vagus centers.

(*d*) Irregularities from poisoning of the heart muscle, which may pass into fibrillation.

(*e*) In the frog's heart, aconitin when applied directly may cause (1) slowing, (2) quickening, (3) slowing, (4) quickening.

1. Due to vagus stimulation of vagus-endings.
2. Due to muscular stimulation.
3. Incoördination leading to paralysis.
4. Complete incoördination passing into fibrillation or peristalsis.

This peristalsis is characteristic.

(*f*) Aconitin is a general protoplasmic poison, but it will kill from a central action before this is seen.

Experiment I.—(*a*) Inject 0.5 c.c. of 0.1 per cent. aconitin into the lymph sac of a frog (Fig. 25). Compare this with another frog:

(*b*) Into which 0.5 c.c. of 5 per cent. infusion of digitalis is injected in the same way.

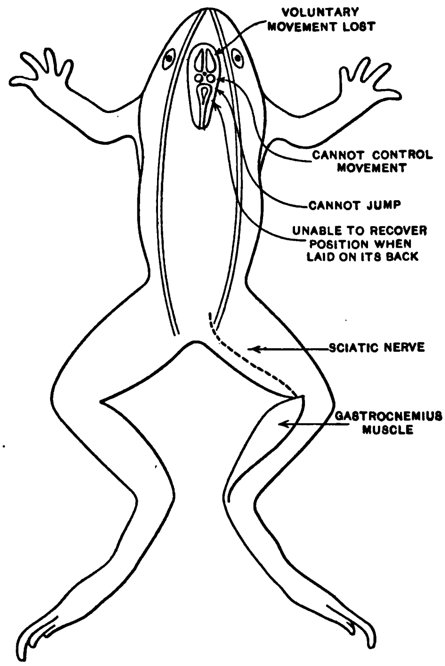


FIG. 26.—To show location of different parts of the brain and effects of their ablation, also the location of the sciatic nerve and the gastrocnemius muscle. (Modified from Dixon.)

Experiment II.—Pith a frog and take heart tracings by the suspension method. Inject 1 c.c. of 0.1 per cent. aconitin into the anterior lymph sac and take continuous tracings until the heart is paralyzed.

Experiment III.—Take a continuous tracing of the blood-pressure and respiration of a dog. Give an intravenous injection of 0.5 c.c. of 0.1 per cent. aconitin every ten minutes until the animal dies. Keep a complete record of the symptoms.

Experiment IV.—Count respiration and heart-rate of a dog. Give 1 c.c. of 0.1 per cent. aconitin intravenously without anesthesia and record result on heart-rate, respiration and general condition.

Experiment V.—*Squibb's Test for Aconitin.*—Dilute tincture of aconitin 1 to 70. Hold 4 c.c. of this in the anterior of the mouth for one minute and discharge it. A distinct tingling will be apparent in from ten to fifteen minutes. Note that the aconitin group of drugs is the only one which, when taken systemically, has a selective action on the sensory nerves.

Experiment VI.—*The Bio-assay of Aconitin.*—Method, U. S. P., ix, p. 606. The method of the physiological assay of aconitin consists in determining the minimum lethal dose for guinea-pigs.

Method.—Select guinea-pigs, 250 to 350 grams weight, in a healthy condition.

Drug.—The tincture, extract or fluidextract may be used.

Administration.—The drug is administered hypodermically. If the extract is used it must be prepared in a liquid form suitable for injection. After injection the animals are placed in cages and in twelve hours note is taken of those living and dead.

Standard.—The standard fatal dose is as follows:

Fluidextract	0.00004 c.c.	per kilo of body	weight.
Tincture	0.0004 c.c.	"	"
Extract	0.00001 gm.	"	"

In making the test a series of animals is used, varying the dose on each side of the standard dose until the dose of the preparation to be determined is ascertained.

THE NITRITES.

The important action of the nitrites is on the circulation.

Experiment I.—*Action of Nitrites on the Circulation and Respiration.*—(*a*) Anesthetize an animal and prepare for blood-pressure and respiratory tracings. Place a cannula in the femoral vein for intravenous injections. Isolate the vagus, stimulate and take tracing.

(*b*) While taking normal tracings let the animal inhale a little amyl nitrite through the trachea. Allow the pressure to become normal. Stimulate the vagus and let the animal again inhale amyl nitrite, and when pressure is at the lowest point again stimulate the vagus.

(*c*) Inject 1 to 10,000 epinephrin; note the height to which the pressure rises, and when the pressure is high again stimulate the vagus. Study the activity of the vagus at high and low pressures. Continue the administration of amyl nitrite as in (*b*) and note whether or not it is as effective after several exhibitions.

(*d*) Take a sample of blood and note the color—methemoglobin. Study with the spectroscope.

(*e*) When amyl nitrite fails to cause a reduction of pressure, inject 1 c.c. of 1 to 10,000 epinephrin and compare the height to which the pressure rises with that of the injection under (*c*).

Experiment II.—Prepare animal as in 1. In this experiment use nitroglycerin.

(*a*) Take normal tracings. Inject 1 c.c. of 1 to 10,000 epinephrin; when the pressure is normal, inject 1 c.c. of 0.1 per cent. nitroglycerin intravenously. Isolate and stimulate the vagus.

(*b*) Repeat injections of nitroglycerin until the effect is relatively small. It may be advisable to double the dose of the nitrite in the latter injections.

(*c*) Examine the blood with spectroscope (see Figs. 55 and 56.)

(*d*) Stimulate the vagus when pressure is at its lowest and compare with the initial effect.

(*e*) When the pressure falls but little on administration of the nitrites give 1 c.c. of 1 to 10,000 epinephrin and compare with the first effect. If epinephrin fails to act or is much weaker in its action, how is it to be explained?

Experiment III.—Repeat Experiment II, using 0.1 per cent. sodium nitrite, giving 0.5 to 1 c.c. intravenous doses.

Experiment IV.—Anesthetize a dog and prepare for records as in Experiment I. Take normal records. Give the animal 1 c.c. of 0.5 per cent. atropin. Repeat 1. After atropin, compare results with those in which atropin was not used.

Experiment V.—Students may experiment on themselves as follows: (*a*) In sitting position with arm on the table, take the normal pulse record with a standard sphygmograph.

(*b*) Break an amyl nitrite pearl in the handkerchief and inhale the fumes.

(*c*) Take pulse tracings again, immediately, in five minutes and in ten minutes. Study the effects which follow the use of amyl nitrite.

Experiment VI.—*Action of Nitrites on Frogs.*—Inject into the lymph sac of frog number:

1. 0.5 c.c. of 0.1 per cent. nitroglycerin.
2. 0.5 c.c. of 0.1 per cent. amyl nitrite.
3. 0.5 c.c. of 1.0 per cent. sodium nitrite.

Record the effects.

Experiment VII.—*Influence of Nitrites on the Bloodvessels. Perfusion Experiments; Lewen-Trendelenburg Method* (Figs. 23 and

24). Pith a frog or small turtle. Fix to board. Tie a fine cannula in the aorta for perfusion; insert a fine cannula in the large median abdominal vein. Perfuse with Ringer's solution through the aorta and count the drops from the vein. If it is difficult to get a cannula in this vein, so that you fail, cut the vein and elevate the animal and the drops may be counted without the

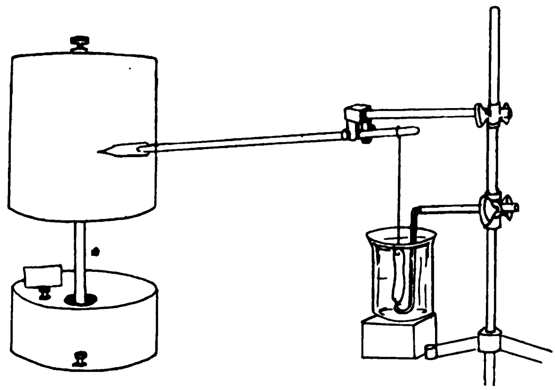


FIG. 27.—Arrangement of apparatus for recording contractions of turtle heart strip. The same arrangement will do for uterine strips if temperature and aëration are controlled.

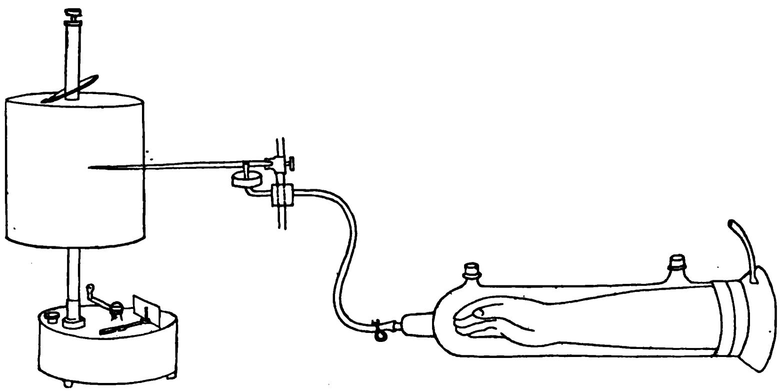
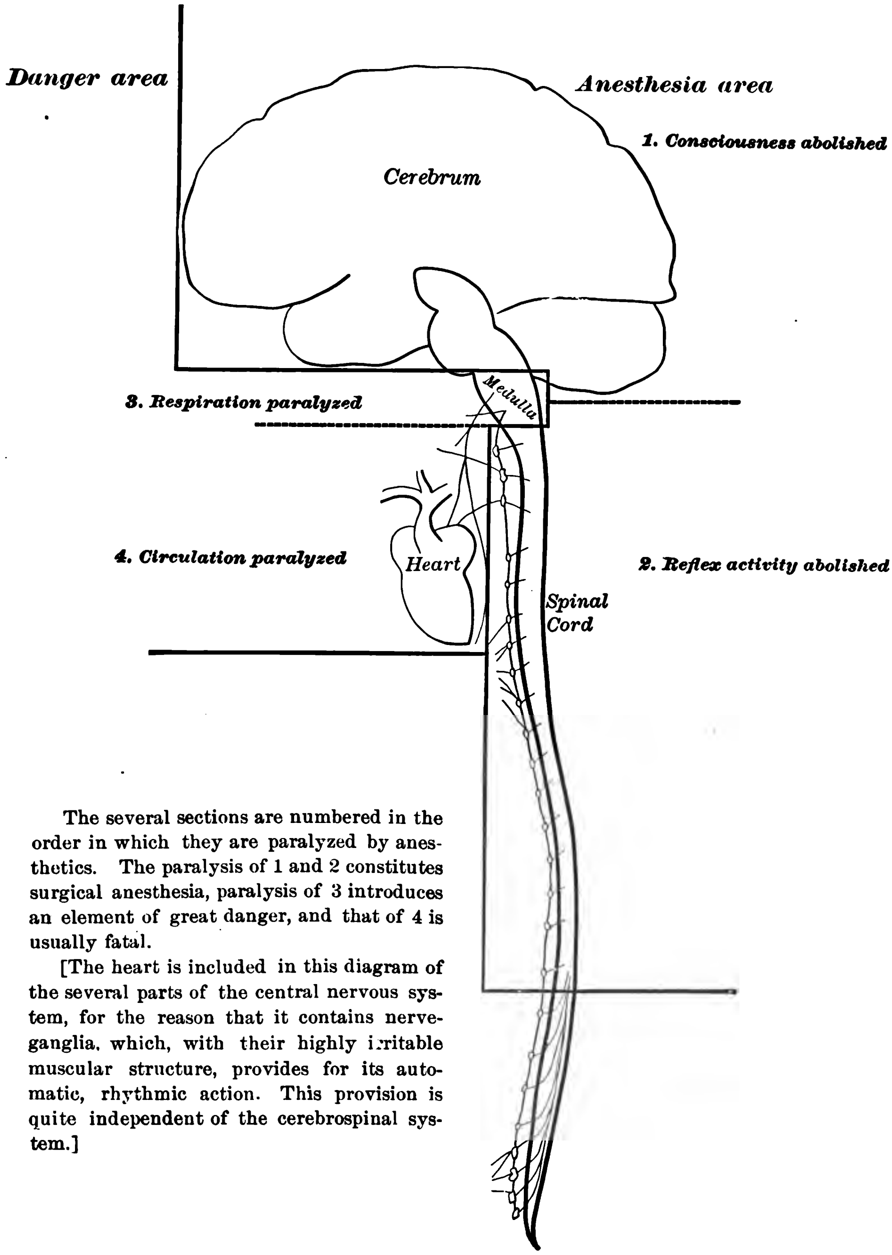


FIG. 28.—Plethysmograph for the study of changes in volume of the arm.

cannula. When the normal is obtained, add to the Ringer solution enough sodium nitrite solution to make 0.01 per cent. sodium nitrite and measure the change in the rate of flow either in drops per minute or in volume.

Experiment VIII.—Action of sodium nitrite on the contracting ventricular strip may be demonstrated as follows: Set up a strip

PLATE IV



The several sections are numbered in the order in which they are paralyzed by anesthetics. The paralysis of 1 and 2 constitutes surgical anesthesia, paralysis of 3 introduces an element of great danger, and that of 4 is usually fatal.

[The heart is included in this diagram of the several parts of the central nervous system, for the reason that it contains nerve-ganglia, which, with their highly irritable muscular structure, provides for its automatic, rhythmic action. This provision is quite independent of the cerebrospinal system.]

and take a normal tracing. When the strip beats rhythmically add 0.02 per cent. sodium nitrite (Fig. 27). What is the proof that nitrites act on the vessel wall directly? Compare the action of epinephrin, ergot, nitrites and barium on the bloodvessels.

Experiment IX.—Take a normal tracing with the arm in a plethysmograph (Fig. 28). After five minutes break and inhale a three- or five-minim ampoule of amyl nitrite and again record for five minutes.

THE ACTION OF THE ALCOHOL CHLORAL GROUP ON THE PUPIL, HEART AND REFLEXES.

On two series of frogs, perform the following experiments, noting especially the condition of the reflexes, the size of the pupil and the condition of the heart at the end of the experiment. One group of students will work with one series of frogs and the second group with the second series, taking care to select specimens for both groups of about the same size. Injections will be made in the anterior lymph sac. The dose will be varied as follows:

Frog No.	Group I.	Group II.	Drug.
1 . . .	1.00 c.c. (25 per cent.)	2.00 c.c. (25 per cent.)	Alcohol.
2 . . .	0.10 c.c.	0.30 c.c.	Chloroform.
3 . . .	0.50 c.c.	1.00 c.c.	Ether.
4 . . .	0.25 c.c.	0.75 c.c.	Paraldehyde.
5 . . .	0.50 c.c. (10 per cent.)	2.00 c.c. (10 per cent.)	Urethane.
6 . . .	0.50 c.c. saturated water solution	2.00 c.c. saturated water solution	Chloreton.
7 . . .	1.00 c.c. (2 per cent.)	2.00 c.c. (2 per cent.)	Chloral.
8 . . .	1.00 c.c. (4 per cent.)	2.00 c.c. (4 per cent.)	Morphin.
9 . . .	Control	Pith brain and cord.	

At the end of one hour pith all the animals, expose the heart by a small incision and make record tracings of each on the same drum for comparison.

State the condition of the heart, pupils and reflexes.

Reflex Time as Changed by Alcohol.—1. What is the function of reflexes?

2. Their importance in every-day life?

3. The modification of reflexes by the alcohol group of drugs?

4. How are reflexes tested?

Experiment I.—Türck's method of determining reflex time (see Fig. 13.) Pith a frog waiting twenty minutes for recovery from shock and suspend it by the head with a clamp. With a small beaker containing 0.5 per cent. HCl or H_2SO_4 immerse the toe or foot to a definite point. Note the time of withdrawal by a stop-watch. Wash off

the acid with another beaker containing water. Repeat the process until five concordant results are obtained and take the average. Now take the frog from the position and inject 0.5 c.c. of 25 per cent. alcohol into the anterior lymph sac. In fifteen minutes repeat the determination of reflex time. Repeat the injection of alcohol and the determination of the reflex time until a definite change is obtained.

Experiment II.—*Crossed Reflex Time* (Fig. 29).—In this experiment the possibility of direct stimulation on axon reflexes is ruled out. The movement when obtained is decisively reflex.

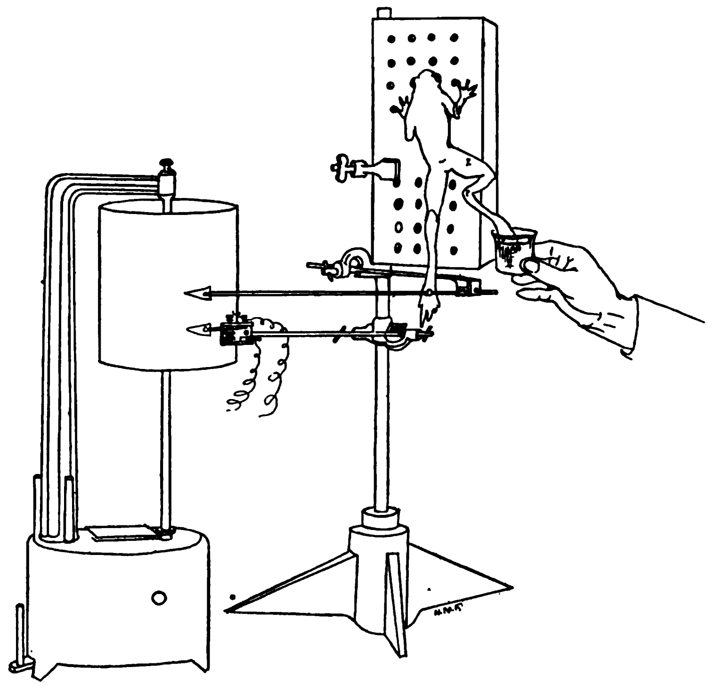


FIG. 29.—Method of taking crossed reflex.

Pith a frog as above. Wait fifteen minutes for recovery from shock. Suspend the animal by the head with a muscle clamp. Attach the toe of the foot to a muscle lever to write on a slowly moving drum. Arrange a signal magnet to write below the muscle curve. Insert thin wire electrodes from a secondary induction coil into the skin of the other leg and tie the foot so that this leg cannot move. Adjust the induction coil to produce a stimulus that will give a distinct cross reflex movement. Take the time of the

movement with a stop-watch or from a time mark record on the drum. Get the average of five determinations. Have the time of these determinations sufficiently far apart to eliminate the probability of fatigue playing a role. When the normal is obtained inject alcohol 0.5 c.c. of 20 per cent. into the dorsal lymph sac and after ten minutes or more repeat the determination. Repeat injections of alcohol every thirty minutes until a definite change in the reflexes is obtained. These experiments may be repeated, using 3 to 5 drops of ether, 3 drops of chloroform, or 1 c.c. of 2 per cent. chloral hydrate.

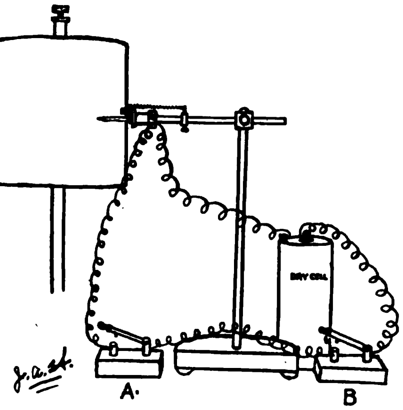


Fig. 30.—Arrangement of apparatus for recording reflex time. (After Jackson.)

Experiment III.—*Effect of Alcohol on the Reaction of the Student.*—The following experiment, devised by Jackson, will show the change in the reaction time in human beings:

1. Reaction of *sight* as affected by alcohol. Arrange a signal magnet to write on a swiftly moving drum. Connect this magnet with a cell and in the circuit place two keys or switches. When either key is opened the circuit is broken and the result is indicated on the drum. Two students work this experiment.

One, the operator, holds key B, while the other, the subject, whose reaction is to be tested, holds key A. The man at key A keeps his attention centered on the signal magnet, which is writing on the swiftly moving drum. The operator closes key B, which causes the writing-point of the signal magnet on the drum to fall. The subject opens key A as soon as he sees the fall of the writing-point. While the drum keeps running, B is opened by the operator and key A is closed by the subject at once.

Key B is again closed and A opened, etc., as rapidly as the sub-

ject perceives the movement of the needle caused by the opening or closing of B until from twenty to thirty records are made.

The average time of the sight reaction is obtained as follows: An electric tuning-fork, vibrating from 50 to 100 times a second, is used to run a time tracing around the drum parallel to the reaction time record. A rule or pair of dividers is used to measure off the time for each reaction and an average for normal sight reaction is then calculated.

The next step after determining the time for normal reaction is to determine the time for sight reaction after alcohol has been administered. Five to 10 c.c. of alcohol or whisky or brandy, well diluted in water, and sweetened to render the liquor more palatable, are taken into the stomach by the subject. After fifteen minutes the same process as that described above is repeated and the results of the two tests compared, to show the effect of alcohol on the time reaction of sight.

Ether and Chloroform Anesthesia.[1]—The student should be able to explain the effect and the nervous mechanism in each case.

The symptoms are conveniently divided into four stages:

I. *Preliminary or Stage of Disorganized Consciousness and Analgesia.*—Struggling due to:

1. Irritant action on mucous membranes, and this causes:
2. Reflex effects:
   Coughing.
   Salivation and flow from respiratory mucous membrane.
   Respiratory inhibition and irregularity.
   Cardiac effects.
3. Disturbances of judgment.
4. Loss of memory and self-control.
5. Emotional tendencies.
6. Disturbances of special senses less acute; hissing and roaring sounds.
7. Analgesia.
8. Vertigo and ataxia.
9. Quickened pulse and rise of blood-pressure, probably asphyxial.
10. Increased respiration.
11. Dilated pupils.

[1] As arranged by Dixon: Manual of Pharmacology.

II. *Narcotic Stage and Unconsciousness:*
1. Coughing, retching, vomiting.
2. Delirium, muttering to shouting.
3. Tonic and clonic muscular spasms.
4. Reflexes diminished but still present.
5. Unconsciousness.
6. Respiration irregular from struggling.
7. Pulse accelerated and pupil dilated, both from excitement.

III. *Surgical Anesthesia:*
1. Muscular relaxation.
2. Loss of reflexes.
3. Breathing slower and regular snoring.
4. Decrease in respiratory exchange.
5. Fall of blood-pressure and temperature.
   Dilatation of skin vessels.
   Lessened movements.
   Heat center uncontrolled.
6. Smaller pupil does not react to light.

IV. *Stage Leading to Bulbar Paralysis—Toxic Stage:*
1. Loss of bladder and rectal reflexes.
2. Paralysis of vasomotor center; fall of blood-pressure.
3. Paralysis of respiration center.
4. Pupils dilated.
5. Depression or paralysis of cardiac muscle.

The action of alcohol, ether, chloroform and chloral differs mainly in the degree of action. In working with one of these, it is well, to compare the results of all.

The chief actions are exerted on or manifested by:
1. The central nervous system.
2. Respiration.
3. Heart.
4. Muscular work.
5. Reflex time.
6. Eye.
7. Local action.
8. General protoplasmic action.

The uses of alcohol in medicine aside from solvent and preservative purposes are:
1. Its local and irritant action.
2. Its action on the central nervous system.
3. Its value as a food.

Ether, chloroform and chloral are not oxidized in the body, hence their use in medicine depends on the first two properties. (*Cf.* Alcohol.) Study the absorption, local action, fate and excretion of these drugs.

In the action of all drugs, part of the action is objective, part subjective. In animal experimentation it is apparent that the objective side of the action is emphasized.

The above table, slightly modified from Dixon, gives the symptoms of ether and chloroform anesthesia. Note the symptoms and the stages carefully, and study especially the explanations of these symptoms.

Experiment I.—*Action of Alcohol on a Normal Dog.*—Before administering a drug, always note the weight, sex, appearance, heart-rate, character of pulse, eye, size of pupil and reflexes, condition of muscles, temperature, etc., as outlined on sheet.

With a stomach tube introduce 5 c.c. per kilogram of body weight of 50 per cent. alcohol. Make complete observations and records. Repeat observations and records every ten minutes for one hour. At the end of this time anesthetize the animal with ether or chloroform. Note the symptoms closely and compare the symptoms of anesthesia in an animal drunk with alcohol, with the symptoms produced in the anesthetization of a normal dog.

Experiment II.—In a second animal, for comparison with the first, make complete observations and records. Then give the animal 1 c.c. of 50 per cent. alcohol per kilogram of body weight. Note and record symptoms every two to five minutes. Compare with dog 1 and explain differences.

Experiment III.—*Ether Anesthesia.*—1. Make and record complete observations, hold the animal in the usual way or tie him securely on an operating board quietly and gently so that no pain or excitement is caused.

2. Record observations again.

3. Place an etherizing cone in the usual way over the nose of the animal and drop ether on the cone at the rate of about 10 drops per second. Continue this rate until the animal is completely anesthetized. Make complete observations and records every two minutes. See whether or not you can distinguish the stages of anesthesia as outlined by Dixon. If any of the symptoms cannot be observed, discuss and explain as far as possible.

Compare the action of ether with the action of alcohol.

When the surgical anesthesia is complete, remove the ether and allow the animal to come out partially. When he reaches the excite-

ment stage, again administer the ether as before. Continue to administer the anesthetic gradually, increasing the rate if necessary until the animal reaches the fourth stage and respiration is about five per minute. Make complete observations and records at this time. Remove the cone and untie the animal and allow him to recover, making complete records every five minutes during this period. After twenty-four hours make another set of records.

Compare the symptoms of ether anesthesia with alcoholic intoxication.

Experiment IV.—Repeat Experiment III, using chloroform instead of ether.

Experiment V.—*Effect of Alcohol on Frogs.*—1. With a hypodermic syringe inject into the anterior lymph sac of a frog 2 c.c. of 50 per cent. alcohol. Place the animal under a battery jar or wire basket on a piece of moist cotton and make observations on the reflexes and pupils every five minutes for thirty minutes (Fig. 25.)

2. On a second frog repeat observations using 1 c.c. of alcohol. Place the animal in a cylinder filled with water and inverted in a vessel of water so that the cylinder contains no air. Compare and explain the behavior of this animal with that of a normal frog.

3. On a third animal use 0.5 c.c. alcohol. Note the condition of the reflexes and the size of the pupil.

After the observations are complete, place the animals in a tank and observe at the end of twenty-four hours.

Experiment VI.—*Effect of Alcohol on Reflex Time.—Reaction Time.*—Instruments needed; a kymograph, a muscle lever, a signal magnet, probe and scissors.

Method:

1. Pith brain and medulla of frog. Wait fifteen to twenty minutes to allow recovery from shock.

2. Adjust kymograph to run about 2 cm. per second.

3. Attach muscle lever and signal magnet about 3 cm. below it.

4. Insert electrodes from the secondary coil into the skin of the frog; adjust induction coil so as to produce minimal stimulus, given a crossed reflex in about two seconds.

5. Proceed to obtain crossed reflex time, taking average about of five.

(*a*) Normal.
(*b*) 0.5 c.c. of 20 per cent. alcohol into dorsal lymph sac.
(*c*) After five to ten minutes' rest repeat (*b*) and 4.
(*d*) After thirty minutes' rest repeat (*b*) " "
(*e*) After sixty minutes' rest repeat (*b*) " "

N. B. Differentiate between direct response to stimulus and crossed reflex when both appear.

Take tracings below one another.

Between each tracing rest about two minutes, to avoid fatigue.

In a second frog prepared in the same way, test the reflex time obtained by dipping the toe into 0.5 per cent. HCl or acetic acid. Dip the toe into the acid, the same amount each time, and note the time taken to withdraw the toe. The time can most conveniently be measured by a stop watch.

Conclusion. Record your results in table form.

Questions. 1. On what side of the reflex arc do these drugs act?

2. In what way may drugs effect response?

3. What is the significance of your results as applied to everyday life?

4. Explain the coughing under ether, the vertigo, salivation, dilated pupils, loss of reflexes, etc., throughout the four stages.

Experiment VII.—*Effect of Alcohol on the Heart of a Frog.*—1. Pith a frog both brain and cord. Expose the heart. Attach a writing lever to the heart by the suspension method.

2. Take a normal heart tracing. (Drum moving 1 cm. in ten seconds.)

3. Drop 5 per cent. alcohol on the heart in a steady stream and continue the tracing. If there is no action use 10 per cent. alcohol.

4. When the action is very pronounced, irrigate the heart with Ringer's solution.

5. On the same animal repeat experiment, using a saturated solution of ether in Ringer's solution.

6. On the same animal repeat experiment, using a saturated solution of chloroform in Ringer's solution.

7. Add a solution of 1 to 1000 adrenalin to the heart when it is almost stopped.

8. Tabulate your results.

Normal heart:

(*a*) Rate.

(*b*) Amplitude.

Alcoholized heart:

(*a*) Rate.

(*b*) Amplitude.

9. From your experiment, can alcohol be used as a heart stimulant? If the results are not definite use weaker or stronger solutions of the alcohol.

THE EFFECT OF GENERAL ANESTHETICS ON THE CIRCULATION, RESPIRATION AND TEMPERATURE.

Outline of study of drugs on heart:

I. Heart Rate, influence of drugs on, chronotropic influence; irritability of the muscle tissue, bathmotropic influence; conductivity of the tissue, dromotropic; force and energy of contractions; inotropic influence manifested by the blood-pressure and the pulse-pressure.

II. Vessels: Constriction; dilations.

Record weight, character and rate of respiration and heart beat, rectal temperature, and general appearance of the dog or rabbit.

1. Induce surgical anesthesia with ether. Insert tracheal cannula and the cannula for the blood-pressure. Insert cannula in the femoral vein for injections. Record respiration and blood-pressure on a drum moving about 2 cm. in ten seconds. Get complete records for a period of ten minutes. Push the anesthetic gradually until the animal breathes about ten times per minute. Note carefully blood-pressure and the condition of the heart at this time and compare the influence of other anesthetics on the heart and blood-pressure when the respiration is slowed to the extent that it is in this case.

2. Remove the ether and connect the tracheal cannula with the nitrous oxide apparatus. Adjust this so that the mixture of nitrous oxide and air will produce anesthesia. Take records and continue for ten minutes. Remove the apparatus and take records as the animal is coming out. When this occurs, administer ether again until the blood-pressure and the respiration is constant.

3. Replace the ether by ethyl chloride. This can be done by spraying the ethyl chloride into a bottle connected with the tracheal cannula. Continue the ethyl chloride for ten minutes and take a complete set of tracings. Allow the animal to come out; take tracings during the recovery. Compare the time of recovery from ethyl chloride and nitrous oxide.

4. Administer ether again and push it gradually until the animal breathes about ten times per minute. Take tracings and records at this time. Allow the animal to come out; take records as before. Again administer ether until the respiration and blood-pressure are constant.

5. Give chloroform by the drop method (see Fig. 2), increasing gradually until the animal breathes about ten times per minute. Allow the animal to recover, and take tracings during the recovery.

Then give chloroform again gradually until heart or respiration stops. Take tracing and when pulse is imperceptible open the animal and examine the condition of the heart.

Compare your results and give opinion of the relative influence of the drugs studied on the heart and respiration. How do your results compare with the report of the Hyderabad Commission?

The Direct and Reflex Effect of Ether and Chloroform on the Heart. —Different sections should compare the results of the following experiments. Take complete record of animals.

Experiment I.—Anesthetize a dog with ether. Prepare for blood-pressure and respiration tracings. After tracings have been taken, gradually push the ether until the animal dies. Which stops first, heart or respiration?

Experiment II.—Repeat (I), but use chloroform after the records are commenced.

Experiment III.—Anesthetize with ether as before and commence records of heart and respiration. When records are satisfactory, allow animal to come out, then administer ether quickly, pushing it until the animal dies. Which stops first, heart or respiration? Perform autopsy at once and examine heart.

Experiment IV.—Repeat III, using chloroform instead of ether.

Experiment V.—Repeat III, but before using the ether, inject intravenously 2 c.c. of 1 per cent. atropin. Isolate and stimulate the vagus. After a few minutes stimulate the vagus again. When stimulation of the vagus has no influence on the heart, administer ether rapidly until the animal dies. Which stops first, respiration or heart?

Experiment VI.—Repeat V, but use chloroform instead of ether.

Experiment VII.—Anesthetize an animal with ether. Take rate of heart and respiration. Thoroughly cocainize the nose and throat by washing or swabbing the membranes with 5 per cent. cocain. Allow the animal to recover from the anesthetic and repeat the anesthetization. Does the removal of the irritation of the nasal mucous membranes influence the action of the drug on the heart?

Compare results of this series of experiments with the report of the Hyderabad Commission.

What factors are operative in stoppage of the heart under anesthesia?

How would you prove that reflexes play a part?

Questions regarding the action of alcohol on the central nervous system:

1. What is the main action of the alcohol group of drugs on the central nervous system?

2. Compare the action of the alcohol group—methane group—and the aromatic series on the central nervous system.

3. How would you prove that a drug stimulates the psychic functions, motor functions and sensory functions of the central nervous system?

4. Compare the action of alcohol, atropin, strychnin, picrotoxin caffein, digitalis and morphin on the central nervous system.

5. What is the fate of alcohol, ether, chloroform, benzene, benzine and strychnin in the body?

6. What is the proof that a drug stimulates the motor areas? How do you explain the increase in motion in some phases of alcoholic intoxication? Compare and explain the action of alcohol, cocain and atropin on these functions.

7. Differentiate alcohol intoxication, morphin poisoning and cerebral hemorrhage.

8. Compare and explain the action of alcohol, chloral, morphin and the eserin pilocarpin group of drugs on the eye. What drugs acting centrally contract or dilate the pupil?

CHAPTER VIII.

THE CLOSED METHOD OF ANESTHESIA.

THE closed method of anesthesia has been developed by Jackson.[1] The method consists essentially in having the animal breathe from a closed vessel containing a small amount of air. The exhaled CO_2 is absorbed by a solution of NaOH placed in the bottom of the vessel. The oxygen supply is furnished from an oxygen tank and the stream of oxygen is just sufficient to supply the needs of the animal. It is blown through the NaOH and in this way keeps this solution stirred up so that it will absorb more CO_2.

The advantage of the method is that less ether is required, but whether or not it will supercede the older methods is yet to be decided.

NITROUS OXIDE ANESTHESIA ON THE DOG.

A short conical glass, like a short percolater, may be used as an inhaler, and can be made to fit the animal's head by means of gauze. It need not be air-tight. Turn on the gas and keep the bag moderately filled until anesthesia is induced. Dogs are rather resistant to nitrous oxide. As soon as anesthesia is complete, take observations as under ether. Allow the animal to come out and compare the return to consciousness with that from ether and chloroform.

The animal may again be anesthetized with gas and ether started while the animal is still under the influence of the nitrous oxide. Compare the animal anesthetized with ether in this way with one that was commenced with ether.

NITROUS OXIDE ON FROGS.

Demonstration.—1. Place a frog in a large-mouthed bottle or other suitable vessel and insert a two-holed stopper, with glass tubes inserted, for administration of gas and exit. Protect the animal from the direct force of the gas. Sufficient NaOH should be exposed in the bottle to absorb CO_2. It should not come in contact with the animals.

[1] Journal of Laboratory and Clinical Medicine, 1916, ii, 94 and 145.

2. Allow the animal to recover and note the time.

3. Anesthetize again and instead of allowing the animal to come out normally, administer oxygen.

4. Try the influence of oxygen alone on a normal frog.

5. Remove the frog and repeat experiment with a guinea-pig or mouse.

6. Compare the action of nitrous oxide on the warm- and cold-blooded animals by placing them both in the bottle together. Notice the difference in the rapidity of anesthesia and the rate of recovery.

If it is desired to know the effect of pressure on these animals a manometer may be attached.

THE SPECIFIC ACTION OF NITROUS OXIDE.

If carbon dioxide is available its action should be compared with nitrous oxide. It was formerly thought that the entire action of N_2O was due to asphyxia. Paul Bert proved that N_2O has a specific action. He mixed 80 parts of N_2O and 20 parts of oxygen, compressed the mixtures $1\frac{1}{4}$ atmospheres and found that in this way nitrous oxide would produce and continue anesthesia indefinitely. Eighty per cent. of nitrous oxide and 20 per cent. of oxygen compressed $1\frac{1}{4}$ times gives eighty volumes, the same volume as the original N_2O. While the animal is inhaling the N_2O it gets as much oxygen as there is normally in the air. The resulting anesthesia, therefore, cannot be due to asphyxia.

This experiment may be more easily, if less accurately, carried out by a nitrous-oxide machine by setting it to deliver 80 parts of nitrous oxide and 20 parts of oxygen. If this gas is administered to an animal in a vessel provided with an outlet there is no need of the NaOH to absorb the CO_2.

BROMIDES.

General Actions.—1. A specific depressing effect on the nerve cells of the central nervous system, motor and sensory.

2. A salt action in greater concentrations.

3. During the elimination of the drug by the skin, an irritant action with eruptions may ensue. This is especially prominent on the head and shoulders.

4. In prolonged use or after large doses there is an irritant action of the stomach, with nausea and vomiting.

5. The collective untoward symptoms are known as "bromism." Most prominent are nausea, vomiting, skin eruption, pigmentation of the skin, sleepiness, mental dulness, muscular weakness and unsteady gait. Compare the action of alcohol, morphin, bromides and cannabis on the heart, respiration, central nervous system, digestive tract, eye and kidney.

Experiments or Demonstrations.—In a series of cats or rabbits, treat the individuals as follows:

1. Give 3 grams per kilo body weight of sodium or potassium bromide in solution by stomach-tube and note the effect.
2. Give the same amount of bromide as in 1. Repeat in two hours if there are no symptoms. An hour after the second dose give 10 c.c. of 20 per cent. camphor in oil per kilo of body weight by stomach-tube.
3. Give this animal 10 c.c. of 20 per cent. camphor in oil per kilo of body weight, and note the results for two hours. What is the action of the bromide in controlling epileptoid convulsions produced by camphor?
4. Dissolve 0.5 gm. of sodium or potassium bromide in 100 c.c. of water. Add chlorin water and shake in a separatory funnel with 25 c.c. of chloroform. A yellow to orange color should be imparted to the chloroform. Compare this color with the following test:
5. Collect a sample of urine and make a test as in 4.
6. Take 1 gm. of potassium or sodium bromide dissolved in 100 c.c. of water. In two hours collect the urine and apply the test as in 4.

CANNABIS.

Cannabis is so unreliable in its action that little satisfactory work can be done with it in the laboratory. It is, however, one of the biological standardized drugs of the Pharmacopœia. The method which is crude at best, consists in administering the drug to dogs in the form of a capsule, 0.004 gram of the extract of 0.03 c.c. of the fluidextract or 0.3 c.c. of the tincture per kilo of body weight; this should produce symptoms of incoördination.

Experiment I.—Weigh a dog and prepare a capsule containing 0.004 gram per kilo body weight of the extract of cannabis. Hold the animal's head back, withdraw the tongue and place the capsule back as far as possible. Release the tongue and hold his mouth shut; slap the throat lightly, if necessary, to make the animal swallow. Watch the animal for two or three hours.

Experiment II.—A corresponding amount of the tincture may be administered in capsule or the solution may be dropped on the back of the tongue from a pipette. If this can be done satisfactorily it is better than using the capsule, as all uncertainty of solution is avoided. Compare this action with morphin and the bromides.

Experiment III.—Groups of students should take the following doses of cannabis one hour before the evening meal and report the effects next day:

Group	I.	1.0 c.c. of the tincture.
	II.	1.5 c.c. " " "
	III.	2.0 c.c. " " "
	IV.	3.0 c.c. " " "

Assay of Cannabis.—The assay is based on the fact that this drug produces certain symptoms of muscular incoördination. The method consists in ascertaining the dose of the drug to be tested that will produce these symptoms of incoördination in a dog and then adjusting its strength by comparison with a standard preparation.

Fig. 31.—Technic of administering capsules to dog by mouth.

Dogs.—Since the animals differ greatly in susceptibility a number of animals should be tried. As a rule, fox terriers serve well, but any species may do. Two dogs should be provided for each assay. The animals should be at least one year old, healthy and kept under the best sanitary conditions. If used for more than one test, three

days should elapse between tests. The tests should be made in a quiet room and free from excitement, and the animals should not see each other.

Preparation of the Drug.—The fluidextract may be given in soft capsules, or the extract made into soft pills may be used. The standard preparation and the drug to be tested should both be prepared in the same form. The animal should be starved for twenty-four hours in order to hasten absorption. The drug is easily administered by placing on the back of the tongue (Fig. 31). Water may be given to aid swallowing if thought advisable.

The average dose of the standard preparation is given to one dog and a like dose given to the other of the solution to be tested. After one hour both dogs should be examined for symptoms of muscular incoördination. This in most animals consists of a slight swaying movement when the animal stands and some ataxia when it moves about. Observation should be made frequently during the second hour after the administration of the drug. The results obtained from the first test should be confirmed at an interval of not less than three days by repeating the administration, but in the reverse order, *i. e.*, the standard preparation should be given to the dog which received the drug to be assayed in the first trial.

In subsequent tests the doses may be modified so that similar symptoms are produced by each sample of drug. If the preparation to be tested is below standard its dose may be increased, or if above strength its dose may be lessened until the equivalent doses of each is found. The same dogs may be used over long periods of time, even for some years, but occasionally they have to be discarded, as in some cases they seem to learn the effect of the drug and so refuse to stand up. A certain degree of tolerance necessitates larger doses.

Standard.—There is no definite chemical that can be adopted as a standard. A carefully prepared and preserved extract or fluidextract may be used. A standard fluidextract will produce incoördination in dogs when administered in the dose of 0.03 c.c. per kilogram of body weight of the dog. 0.004-gram doses of the extract administered in the same way or 0.03 c.c. of the tincture per kilo body weight will produce similar symptoms.

CHAPTER IX.

ACTION OF STRYCHNIN, PICROTOXIN AND CURARA ON THE CENTRAL NERVOUS SYSTEM.

Study the action of these drugs on the nervous system, and especially changes in irritability and determine the site of action:

Technic.—Take four frogs and number them from 1 to 4.

Experiment I.—Note the general condition, normal movements and response to stimuli. With a glass rod, pencil or similar instrument, determine the slightest stimulus that will make the animal move or jump. Note the position of the animals before, during and after such movement. Keep this in mind so that any change after the administration of the drug may be noted.

(*a*) Into the ventral lymph sac of animal No. 1 inject 0.5 c.c. of 0.01 per cent. strychnin sulphate solution.

(*b*) Into No. 2 inject in the same manner 1 c.c. of 0.01 per cent. strychnin sulphate solution.

(*c*) Into the lymph sac of No. 3 inject 0.3 c.c. of 1 per cent. strychnin sulphate solution. Keep the time of injections and note the onset of change in irritability, tetanus and paralysis. Note especially the type of spasm and compare with

(*d*) No. 4, into which you have injected 1 c.c. of 0.04 per cent. picrotoxin solution. Compare the positions which the legs of the animals assume. Note the tendencies to opisthotonos, emprosthotonos and pleurothotonos.

Experiment II.—When satisfied with observations, determine the seat of action of the drugs as follows: Anesthetize one of the strychnin animals which shows strong convulsions and the picrotoxin animal with ether by placing them under a jar together with a piece of cotton soaked in ether (see Fig. 26). Note the influence of ether on the spasms. When anesthetized, dissect and lay bare the brain and medulla. Isolate also one of the sciatic nerves. Wait for the return of tetanus. When spasms reappear cut the sciatic, which is isolated. If the spasms stop in that leg, where is the probable seat of action? Remove cerebrum and optic nerves and wait for the return of the tetanus. Now remove the cerebellum and medulla and again wait about fifteen minutes. Is there any

difference in the strychnin and picrotoxin animals? Finally pith the cord with a strong wire or pithing needle. What is the result?

Experiment III.—*To Determine the Relation of Sensory Stimuli to the Production of Convulsions.*—Poulsson's experiment:[1] Take one of the frogs already in tetanus and immerse it for a few seconds in a 1 per cent. solution of cocain hydrochloride or in a saturated aqueous solution of chloretone, or paint the entire skin of the animal with 5 per cent. solution of cocain, using a camel's-hair brush. Put the animal in a quiet place, under a bell-jar, and in five minutes, if convulsions are still present, immerse a second time. Place again under the jar and observe for thirty to sixty minutes. If sensory stimulus from without is necessary to elicit tetanus, what would you expect in the present case? If tetanus fails to develop, apply a stimulus to the skin by brushing it lightly; if no result, tap the joints lightly and note the results. Isolate the sciatic on one side and stimulate lightly.

Criticise the experiment. What is the effect of cocain on the central nervous system? See Experiment VIII.

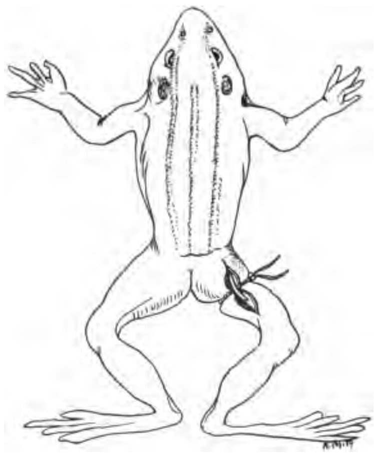


FIG. 32.—Bernard's experiment. The ligature excludes the circulation from the leg while the nerve endings are not influenced by the drug. Curara or other drug may be introduced into one of the lymph sacs.

Experiment IV.—*Claude Bernard's Experiment* (Fig. 32).—*Strychnin.*—Destroy the brain of another frog and protect one hind leg from strychnin by means of a ligature, which will cut off the circulation without injuring the sciatic nerve. Now inject 0.3 c.c. of 0.1 per cent. strychnin sulphate solution into the ventral lymph sac. When

[1] Arch. f. Exp. Path. and Pharm., vol. xxvi, p. 22.

convulsions come on, note whether the non-strychninized leg participates in the convulsions. See whether a convulsion can be initiated by stimulating the protected leg. Compare the curarized frog, one of whose legs has been protected. For comparison with curara, see Curara.

Experiment V.—*Action of Strychnin on Turtle Heart Strips.*—Strychnin on ventricular strips: Suspend a ventricular strip in a measured volume of 0.8 per cent. saline solution and take a record of the beating. When it is beating rhythmically add 5 per cent. solution of strychnin in saline 0.8 until the solution contains 0.01 per cent. strychnin. Take records of this for five minutes and keep adding strychnin until the strip is immersed in 0.2 per cent. strychnin sulphate. What is the direct action of strychnin on the heart muscle?

Experiment VI.—*Action of Strychnin on Mammals.—Demonstration.*—Count the respiration or heart-rate in a rabbit or cat. Give a hypodermic of 0.2 c.c. of 1 to 1000 strychnin sulphate. Note the type of convulsion. Control the spasm with ether. Knowing the method of administration and the action of the drug, how would you treat this case of poisoning? Would the treatment be different if the drug had been given by the stomach? Kill the animal with the anesthetic.

Experiment VII.—*Action on the Heart and Respiration.*—Weigh the animal; count normal heart and respiration rate. Anesthetize with ether or chloroform and again count. Arrange for blood-pressure and respiratory tracings and for injection into the femoral vein. Take a continuous record on a drum moving at about 1 cm. in ten seconds. Inject 1 c.c. of 0.01 per cent. strychnin sulphate per kilo of body weight. Note the effect. Repeat the injection every five minutes until convulsions are elicited. Note the effect on blood-pressure and respiration, especially during the spasm. Control the spasm by pushing the anesthetic. Finally, study the effect of pushing the anesthetic on the heart and respiration. Make use of the animal either for studying the action of corrosive poisons and anesthesia or other work.

On a series of dogs or cats the action of strychnin when applied locally to the central nervous system may be studied as follows: (*a*) The local nature of the action and (*b*) the action of strychnin on the spread of reflexes; (*c*) the modification of the impulse on passage through a strychninized area. These experiments may be done under ether or gas anesthesia.

1. Inject 1 c.c. of 0.2 per cent. strychnin sulphate into the

region of the fourth ventricle after withdrawal of an equal amount of cerebrospinal fluid. Do not keep the animal under the anesthetic longer than necessary. Note the sensitivity of the head and nose while the tail end of the animal is normal. Study the spread of impulses from the head caudalward and from below upward.

2. Inject a second animal with 2 or 3 mg. in the lumbar region.

3. Inject a third animal in the dorsal region. Notice that the region innervated from the strychnin part remains for a long time the long part in which the sensitivity is changed. Note also that impulses pass more readily caudalward than in the reverse direction and that impulses are not changed on passage through the strychninized part.

Compare your results with those of Houghton, Muirhead and Baglioni.

Experiment VIII.—*Synergism of Strychnin and Cocain.*—Take four frogs of the same size. Into the anterior lymph sac of one and two inject 2 c.c. 0.1 per cent. cocain hydrochloride. After thirty minutes inject all with 1 c.c. 0.1 per cent. strychnin sulphate. In which do the spasms first appear? Whether or not this is synergism, or addition reaction is not known.

Experiment IX.—*Caffein.*—Caffein produces convulsions of the strychnin type; inject 1 c.c. of 1 per cent. caffein solution into the lymph sac of a frog. Compare the action with picrotoxin and strychnin. How would you determine that the caffein action in this case is exerted mainly on the cord? Some species of frogs show a typical effect.

Demonstration.—Other Convulsants on Mammals.—Administer to cat or rabbit by the stomach-tube about 20 c.c. total of 20 per cent. solution of camphor in oil (see Fig. 6.) Convulsions usually take place in about a half hour, due largely to stimulation of the medulla. Note that convulsions tend to persist, yet recovery commonly takes place despite the enormous dose of camphor.

Action of Curara on the Central Nervous System of Mammals.—Strychnin when applied directly to motor nerve endings has a curara-like action, but this is not usually seen because the animal dies from a central action before the peripheral paralysis is apparent. Similarly, curara has a strychnin-like action on the central nervous system, but this is not seen if the peripheral paralysis has developed.

Demonstration.—To show the central action of curara, inject 1 c.c. of 0.5 per cent. curara filtered in water into the fourth ventricle and make observations until spasms develop. Note that there is no peripheral paralysis.

In curara poisoning the motor endings are involved before other parts of the reflex arc.

Experiment X.—Ligate a frog's leg high in the thigh with the exception of the nerve. Carefully expose the sciatic on the other side with as little trauma as possible. Inject 0.5 c.c. of 0.1 per cent. curara solution. Just as voluntary motion ceases, stimulate the skin of the poisoned leg; the unpoisoned one will contract. Stimulate the sciatic on the poisoned side; the poisoned muscles will stop contraction before the muscles on the unpoisoned side. The muscles of the unpoisoned side contract when the sensory fibers of the poisoned sciatic are stimulated, owing to reflex stimulation through the cord. This shows that the sensory side of the arc is not affected by the poison while the motor side is poisoned.

Experiment XI.—*The Action of Strychnin on Reaction Time.*—(*a*) Test the reaction time on a frog by the Türck method, using 0.5 per cent. acid.

(*b*) Test the time also when the stimulus is an electric current.

(*c*) Give the animal 1 c.c. of 0.01 per cent. strychnin and wait until spasms appear or until the reflexes show a marked increase.

(*d*) Test the reaction time again.

Is there any relation between the sensitivity of the reflexes and reflex time?

Experiment XII.—*Action of Strychnin on the Ear.*—Determine accurately the distance at which a student can hear the ticking of a watch. Note accurately the position of the subject and the distance of hearing. Now give him $\frac{1}{30}$ grain of strychnin sulphate in solution and in thirty minutes again determine the range of hearing.

Repeat this experiment with a student before and after 0.5 grain of chloral hydrate.

Experiment XIII.—*Action of Strychnin on the Eye.*[1]—Determine the extent of the field of vision for several colors, especially blue, with a perimeter before and after strychnin. Give $\frac{1}{30}$ grain of strychnin sulphate in solution and after thirty minutes again determine the area of the usual field. Compare before and after strychnin.

Questions.—1. How does strychnin influence vision?

2. Compare the actions of morphin and strychnin on the eye.

3. How does atropin, pilocarpin, morphin, strychnin, cocain, epinephrin and silver salts differ in their actions on the eye?

4. Make a diagram of the nerves and muscles, intrinsic and extrinsic, of the eye and locate the points of action of the drugs acting on the eye.

[1] Note size of the pupil of a student, before and after strychnin.

5. From your experiments, where is the site of the action of strychnin? Give reasons.

6. Did strychnin in this case produce any change in spontaneous activity?

7. What changes did strychnin produce in respiration?

8. What change did strychnin produce in the reflexes studied? Do the facts you have noticed indicate where and how strychnin acts to produce this effect? Explain.

9. Are the convulsions dependent upon afferent impulses and if so, what is your proof?

10. Are the convulsions dependent upon changes in the peripheral tissues, motor nerves, sensory nerves or muscles? Proof.

11. Compare the actions of strychnin, atropin, morphin, caffein, bromides, cannabis indica and alcohol on—

(*a*) Central nervous system.
(*b*) Heart and respiration.
(*c*) Kidneys.
(*d*) Intestine.
(*e*) Skin, secretion of drugs by, and influence on, by drugs.

CHAPTER X.

PARALYSIS OF MOTOR NERVE ENDINGS.

Action of Drugs on Motor Nerve Endings in Striated Muscle.

CURARA.

DRUGS that act on nerve-endings may cause either stimulation or depression. The action of a drug on nerve-endings may be determined by studying the function of the nerve before and after the exhibition of the drug.

In pharmacology the action of curara is a classic both because of its definite and easily analyzed action and also because of its value in illuminating the methods of determining the action of a drug. It is not used in medicine.

Curara (arrow poison) is an impure native extract prepared from an unknown species of strychnos. It varies so in strength that the dose cannot be accurately given. Begin with a small dose and repeat every fifteen to thirty minutes until the action is plainly obtained.

Experiment I.—*Action of Curara on Mammals.*—Morphinize and chloroform a dog. Take the blood-pressure and introduce a tracheal cannula to take the respiration by the intratracheal method. Arrange the apparatus to be ready for artificial respiration in case of need. Inject intravenously 5 c.c. of 1 per cent. curara. All movements of voluntary muscles, including the respiratory movements, will stop almost immediately. The heart-rate and the blood-pressure will remain good and by the application of artificial respiration the circulation may be maintained for several hours. If too much of the drug has not been administered it will be eliminated and the animal will recover.

Experiment II.—*The Central Action of Curara.*—Curara given by mouth has no action. The paralyzing action is seen only when it is given hypodermically or intravenously. Curara has also a central action like strychnin. Ordinarily this is not seen because of the peripheral paralysis. If, however, curara is injected into the fourth ventricle of a dog, spasms resembling strychnin soon develop.

Demonstration.—Inject 1 c.c. of 1 per cent. curara into the fourth ventricle and note the effect on the animal for an hour or longer. When satisfied as to the central action, inject the same amount intravenously and watch the effect. Repeat the intravenous injection if necessary.

Experiment III.—To determine whether a motor paralysis is central or peripheral, the sciatic nerve in a frog is exposed and stimulated electrically. If there is no response the paralysis is peripheral. If the muscle contracts the central seat of the paralysis is located by successive stimulation of the cord and medulla and cerebrum, or by ablation in the reverse direction, cerebrum, medulla and cord.

A peripheral paralysis may be in the nerve trunk, the endings or the muscle fibers. No drug is known which has a selective action on the motor nerve trunk when applied systemically. The possibility of this action may be excluded by the curara experiments described below. If the motor endings are paralyzed the muscle will contract if the electrodes are laid directly upon it.

Claude Bernard's Experiment.—1. Observe frog and note whether or not the reflexes are normal.

2. Pith the brain and prevent as little loss of blood as possible. The better the circulation the quicker the absorption. Expose the sciatic on one side in the thigh for half an inch. Pass a strong thread under the nerve and tie tightly around the limb, excluding the nerve. This should stop the circulation in the limb. Inject into one of the lymph sacs 0.5 c.c. of 1 per cent. curara in 0.75 per cent. salt solution. When the paralysis is complete, isolate both sciatics up to the vertebral column. Stimulate the anterior part of the animal with the electrodes and note results. Now lay both sciatics on the electrodes; stimulate. The muscles of the ligatured limb will contract. This proves that the nerve trunks are not paralyzed. Now stimulate the muscles of the poisoned leg directly. This proves whether the muscles are paralyzed or not. Where, then, must the action of curara be located? If the action were on the central nervous system what would be the results of the above stimulation?

Experiment IV.—*Action of Curara on Muscle-nerve Preparation.*—Lay a slide across a small evaporating dish containing the drug dissolved in normal saline; the solution should not reach the slide. Make two muscle-nerve preparations; preserve the entire length of the sciatic nerve in a fresh frog. Lay the muscle of one preparation on the slide, letting the nerve dip in the solution. Lay the nerve of the other preparation on the slide, letting the muscle lie

in the solution. Stimulation of the immersed nerve gives a contraction in (No. 2) as does stimulation of the muscle directly. This proves the nerve fiber is not affected. Stimulation of the muscle in two gives contraction, therefore the muscle is not poisoned. Stimulation of the nerve of two gives no contraction, therefore the muscle is not affected nor is the nerve; the toxic effect of the curara must be between the two or on the nerve endings. Compare this action with fatigue. The order of fatigue is nerve-cell, nerve-ending, muscle.

Demonstration.—Drugs acting similarly to curara when injected into the lymph sac of frogs.

1. All quaternary ammonium bases.
2. Camphor, 0.1 gram in oil or saline.
3. Lobelin, 0.210 gram.
4. Coniin, 0.010 gram.
5. Magnesium sulphate, 1.5 c.c. of 50 per cent. solution.
6. Strychnin—paralytic doses. This does not kill frogs as rapidly as mammals.
7. Methyl strychnin.
8. Amyl quinin.
9. Phosphorus arsenic compounds corresponding to the quaternary ammonium bases.

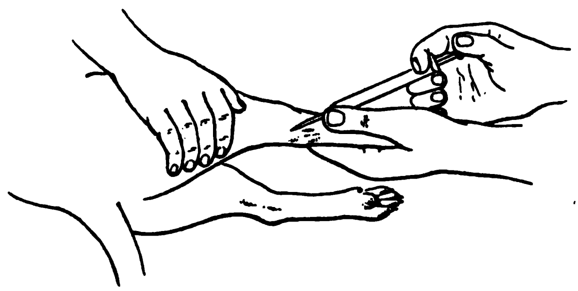


FIG. 33.—Method of injection into the femoral vein. The same method can be used to withdraw blood from the vein.

Experiment V.—*Curara on Non-anesthetized Animals.*—Inject 1 c.c. of 1 per cent. curara into the femoral vein of a dog (Fig. 33.) Observe closely the progress of paralysis. If this dose is not sufficient inject more. When paralysis of the leg muscles is complete give artificial respiration if necessary. The animal may be saved in this way. Physostigmin, 4 to 5 mg. per kilo, has an antidotal effect.

Stimulation of Motor Nerve Endings.—Cholin, guanadin and physostigmin stimulate motor-nerve endings and so facilitate the passage of impulses to the muscles.

Experiment VI.—Inject a dog hypodermically, or very slowly intravenously, with 1 c.c. of 1 per cent. solution of curara and observe the animal for ten minutes. Repeat the injection until complete motor paralysis is apparent. If too much has not been given the animal will recover. Study the symptoms during recovery. In another animal treated in the same way, study the effect of the intravenous injection of 1 per cent. physostigmin in 0.5 c.c. doses.

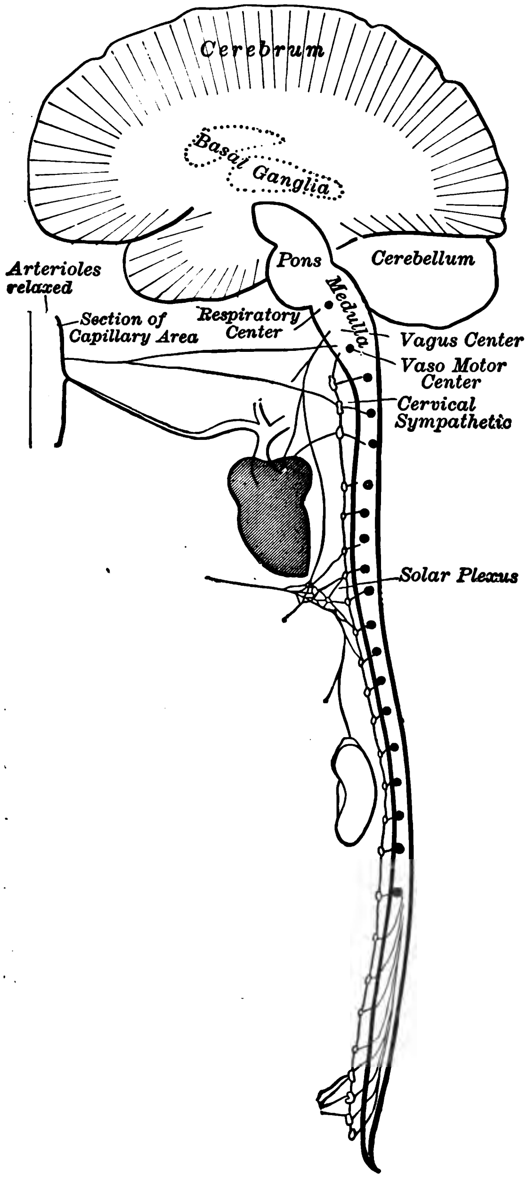
Experiment VII.—Anesthetize a dog. Introduce a tracheal cannula and take respiratory tracing. Take the blood-pressure at the same time. Arrange for artificial respiration when needed. Inject into the femoral vein 0.5 c.c. per cent. curara solution. Repeat this occasionally until the respiratory muscles are paralyzed. When this happens use artificial respiration intratracheally. Now inject intravenously a 1 per cent. solution of physostigmin 0.5 c.c. at a time. This will stimulate the nerve-endings. The animal soon regains the power of automatic respiration.

If too much curara has been given the animal will not recover its power of respiration. Study the influence of the drug on the heart-rate, blood-pressure and respiration. Observe especially the time of cessation of heart and respiration. What are the factors involved in sustaining blood-pressure, and how are these modified by the use of curara?

Note.—Nearly any drug in sufficient concentration will effect nerve fibers if applied directly to them. There is no drug known that shows a selective action for nerve fibers, and when drugs are administered systemically they will cause the death of an animal from an action on some other part before any significant action can be observed on the nerve fiber. Curara in larger doses may influence ganglion cells or other parts of the nervous system, but its main action is on the motor endings to striated muscle.

Since the experiments above definitely locate the action of curara on the nerve-endings, and since physostigmin counteracts the action of the curara, its action is on the same point. (For the probable mechanism of this action, see Meyer and Gottlieb, Dixon, Cushny and Sollmann.)

PLATE V.



The blue color indicates the depressant effects of a toxic dose of Cocaine.

COCAINE.

The poisonous effects of Coca, or the secondary effects of a large dose, are depressant, following quite definitely the lines of previous stimulation.

Nervous System.

Brain. Cerebral functions are first stimulated, then depressed, frequently with production of narcosis or convulsions.

Medulla. Depresses respiratory center and probably vaso-motor center.

Spinal cord. Depresses reflex centers.

Circulation. Arterial pressure is lessened.

Heart. Depressed by direct action of the drug.

Capillary area. Arterioles relaxed, probably through paralysis of vasomotor center.

Eye is dilated. Acts as a nerve block.

Respiration. Depresses the respiratory functions by lessening the irritability of the center in the medulla.

In general, the depressant action is that of a general protoplasmic poison, the commonest evidence of which is its paralyzant influence upon nerve tissue when locally applied. The sensory nerves are more susceptible.

For local analgesic purposes the alkaloid Cocaine is employed in from ½ to 4 per cent. solutions. It acts by blocking the sensory impulses so that they never reach the brain or pain area.

CHAPTER XI.

PHARMACOLOGY OF SENSORY NERVE ENDS.

COCAIN.

ONLY the aconitin group of drugs has an action on afferent nerve-ends (receptive surfaces) when given by mouth or intravenously. The local anesthetic action of cocain is obtained only by the direct application of the drug. It is used in medicine principally for its local action. If sufficient is given systemically the animal dies from a central action before the receptive surfaces are influenced.

Experiment I.—Cut a piece of filter paper about 2 cm. square; dip it in 1 per cent. cocain solution and apply to the side of the tongue. In a few minutes compare the sensitivity of this point with that of the other side.

Experiment II.—(*a*) Place 2 to 3 drops of 1 per cent. cocain hydrochloride in the eye of a rabbit; in a few minutes test the corneal reflex and sensitivity of the eye and compare it with the normal.

(*b*) After injection of cocain, note the size of the pupil and condition of the eyeball. Explain.

Experiment III.—Inject hypodermically into the leg of a dog 0.1 per cent. solution of cocain hydrochloride according to Shleich's method and determine whether you can operate in this part without causing pain.

Experiment IV.—Repeat III, using prococain or other cocain substitute.

Experiment V.—Inject cocain, 0.5 c.c. of 0.5 per cent. cocain hydrochloride into the lymph sac of a frog and note results.

Experiment VI.—Count respiration and heart-rate in a dog. Note condition of the pupil; inject 5 c.c. of 0.5 per cent. cocain intravenously and in five minutes again take records.

Experiment VII.—Take records of the frogs and turtle heart by the suspension method. Irrigate with 0.01 per cent. cocain hydrochloride in normal saline and note results in the tracing.

Experiment VIII.—Prepare turtle heart strips and take tracings of the contractions in 0.8 per cent. NaCl. Replace with saline containing 0.01 per cent. cocain solution. What is the result?

Experiment IX.—Ligate one leg of a frog as high up as possible. Inject 0.5 c.c. of 0.5 per cent. cocain into the dorsal lymph sac. In thirty minutes prepare the muscles of both legs for superimposed tracings, weighting both muscles to the same extent, about 50 grams, and stimulate the nerves by the same electrode. Take tracings on a slowly moving drum and note which muscle fatigues first (see Fig. 25.)

Experiment X.—1. Effect of cocain on the circulation and respiration of a mammal; anesthetize a mammal with ether; insert tracheal cannula and prepare for respiratory and blood-pressure tracings. Inject 1 c.c. of 1 to 10,000 epinephrin. Repeat after five minutes.

2. Inject 5 c.c. of 0.5 per cent. cocain intravenously; note effect on the heart, respiration and eye.

3. In three minutes repeat the injection of epinephrin. Is there any difference in the height or character of the epinephrin curve?

Experiment XI.—*Spinal Anesthesia.*—Without the use of an anesthetic inject 0.1 per cent. cocain or 1 per cent. procaine or any other cocain substitute into the membranes of the cord in the lumbar region of a dog. Use a thin needle. In five minutes test the sensitivity in the hind legs. What are the dangers of spinal anesthesia? Can an animal walk if the feet are anesthetized? Explain.

Experiment XII.—*Action of Cocain on the Temperature.*—Take the rectal temperature of a dog or rabbit. Inject 1 c.c. per kilo of 5 per cent. cocain intravenously in the dog or 2 c.c. hypodermically in the rabbit. Take temperature every ten minutes for four times. If the animal is not in convulsions, repeat the injection until definite symptoms occur. Make a notation of the variation from the normal.

Treatment of cocain poisoning. This is purely symptomatic.

Local Anesthesia in Man.—Sterilize a small hypodermic syringe and needle by boiling. In the same way boil about 10 c.c. of 2 per cent. cocain hydrochloride for two minutes.

Boil needles for testing sensation in the same way. Wash the skin of the arm with soap and water, alcohol, ether and finally paint with tincture of iodin. Inject about 0.2 to 3 c.c. of the cocain solution, under the painted area, with aseptic precaution. In a minute test the sensation to the prick of the needle.

CHAPTER XII.

AUTONOMIC SYSTEM AND AUTONOMIC DRUGS.

THOSE drugs which act especially on the autonomic sympathetic or the sympathetic-parasympathetic systems are known as autonomic drugs. The used nomenclature of this system is not definitely established. At present it is current only among physiologists and pharmacologists. Anatomists are not yet agreed on it, and it is still in a state of change. The classification is based mainly on the reaction of parts of the nervous system to the action of drugs, and these reactions are so striking and constant that they must indicate fundamental anatomical differences. The unstable condition of the nomenclature is due to the newness of this field and the minor changes which detailed investigation always brings.

Langley has done most work on this system and the nomenclature is due for the most part to him. He divides the involuntary nervous system, or the vegetative nervous system, into—

1. Autonomic or parasympathetic.
2. Sympathetic.
3. Enteric system.

The great difference between this system and the *voluntary system* is that in the voluntary system the motor fibers go direct from the anterior horn cells to the end-organ or the effector organ. In the involuntary nervous system the nerve fibers, after leaving the central nervous system, first pass to a ganglion before going to the end-organ. Just why we have control over the organs that receive their nerve supply direct from the central system and have no control over those innervated by the sympathetic is not known. So far as we know there is no reason for the difference.

Differences between the Sympathetic and Parasympathetic System.—The sympathetic system leaves the cord from the first thoracic to the fourth or fifth lumbar. They include vasomotor, sweat, pilomotor and secretory fibers. The system differs anatomically, embryologically, physiologically and pharmacologically from the parasympathetic system.

The Parasympathetic System.—The parasympathetic system is also called the craniosacral autonomic system or the craniobulbar

and sacral sympathetic systems. The fibers forming this system arise from the brain, medulla and midbrain and are carried especially in the third, seventh, ninth, tenth and eleventh cranial nerves. The sacral part of this system leaves the central system mainly in the

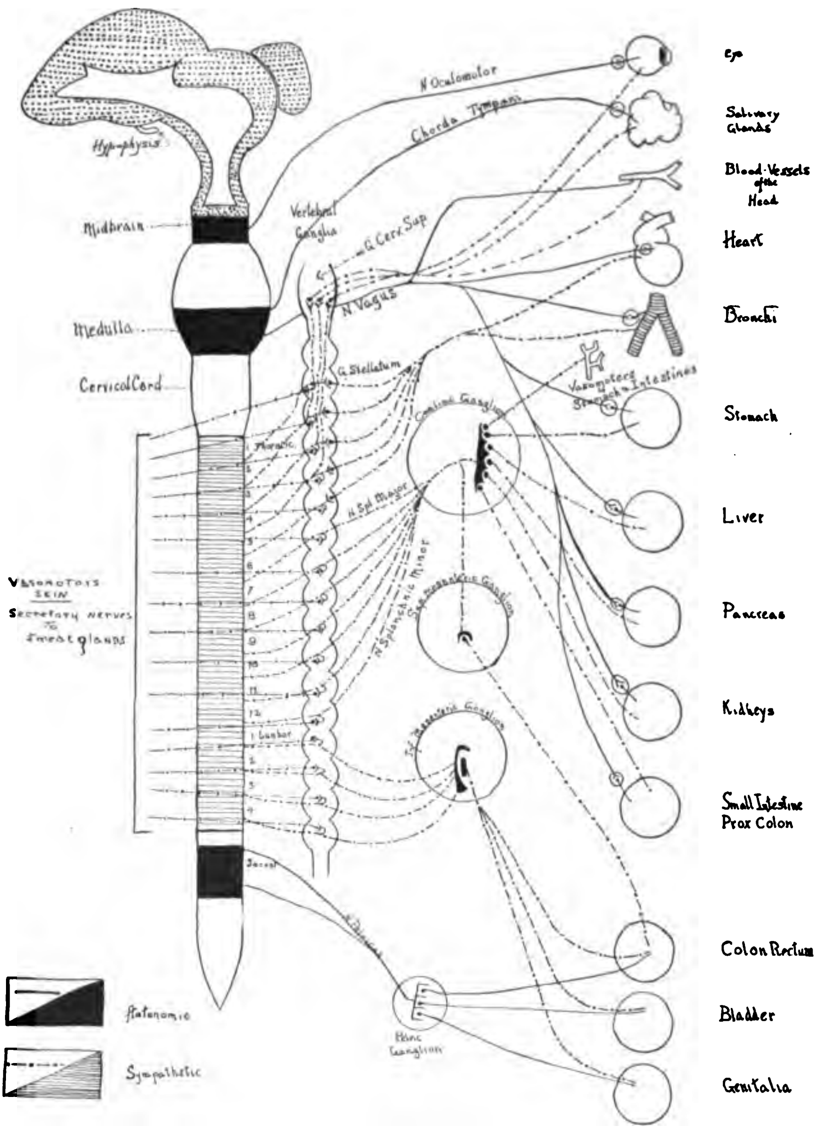


Fig. 34.—Distribution of the various divisions of the vegetative system. Sympathetic fibers are indicated by dotted lines; parasympathetic (autonomic) by unbroken lines. (Kraus, modified from Meyer and Gottlieb.)

COMPARISON OF ANTAGONISTIC ACTIONS OF SYMPATHETIC AND AUTONOMIC SYSTEMS.[1]

Result of stimulation of the sympathetic system.	Action of Atropin.	Action of Adrenalin.	Organ.	Action of Pilocarpin.	Action of Ergotoxin.	Result of stimulation of autonomic system.
Stimulation Th. I–II	Paralysis	Stimulation	Sphincter iridis	Stimulation	....	Stimulation N. III.
			Dilator iridis			
Stimulation Th. I–III	Paralysis	Stimulation	Ciliary muscle	Stimulation	Paralysis	Stimulation N. III.
			Orbital muscle	Paralysis		
Stimulation Th. II–IV	Paralysis	Stimulation ı ?	Salivary glands	Stimulation	....	Ch. tympani. secretion.
		Constriction	Cortical bloodvessels			Dilatation N. X.
Constriction Th. II–IV	Constriction?	Dilatation	Buccal bloodvessels	....	....	Constriction N. IX.
		Constriction	Skin bloodvessels, head region			
Constriction Th. II–IVL	Dilatation	Dilatation	Coronary bloodvessels	Constriction	Dilatation	
		Constriction	Intestinal bloodvessels			
Constriction L. I–IV	....	Constriction	Genital bloodvessels	....	....	Dilatation N. pelvic.
Stimulation Th. II–L. IV	Inhibition	Inhibition	Sweat glands	Stimulation		
Stimulation Th. IV–VII	....	Stimulation	Pilomotor muscles of the face	....	Paralysis	
Stimulation Th. I–V	Stimulation	Stimulation	Heart muscle	Inhibition	Inhibition	Inhibition N. X.
Relaxation Th. II–V	Relaxation	Relaxation	Esophagus	Stimulation	....	Stimulation N. X.
Paralysis Th. II–L. IV	Paralysis	Paralysis	Cardia	Stimulation	....	Stimulation N. X.
Diminished Th. II–L. IV	Diminished	....	Gastric tone	Increase	....	Increases N. X.
Paralysis Th. II–L. IV	Paralysis	Paralysis	Gastric peristalsis	Increase	....	Increases N. X.
Diminished ?	Diminished	Diminished ?	Gastric secretion	Increase	....	Increases N. X.
Inhibition Th. II–L. IV	Paralysis	Paralysis	Small intestine peristalsis	Stimulation	....	Stimulation N. X.
Relaxation L. I–IV	Relaxation	Relaxation	Colon	Stimulation	....	Stimulation N. pelvicus.
Relaxation L. I–IV	Relaxation	Relaxation	Sphincter ani (muscle)	Spasm	....	Spasm N. pelvicus.
Relaxation Th. II–L. IV	Relaxation	Relaxation	Gall-bladder	Contraction	....	Contraction N. X.
Inhibition ?	Inhibition	Inhibition	Pancreatic secretion	Stimulation	....	Stimulation N. X.
Contraction L. I–IV	Inhibition	Inhibition	Bronchial muscle	Stimulation	....	Stimulation N. X.
		Contraction	Sphincter vesicæ			Relaxation N. pelvicus.
Relaxation L. I–IV	....	Relaxation	Detrusor vesicæ	Relaxation	....	Contraction N. pelvicus.
		Contraction	Uterus (pregnant)	Contraction		
		Relaxation	Uterus (gravid)			
Contraction L. I–IV	....	Contraction	M. retractor penis	....	....	Relaxation N. pelvicus.
Sugar puncture	....	Raised	Carbohydrate tonus	Diminished		
Heat puncture	....	Raised	Heat balance			
Contraction	....	Contraction	Pigment cells	Dilatation		

Th. = Dorsal, thoracic segments. L = Lumbar segments. N = Nerve.

[1] Jelliffe and White: Nervous and Mental Diseases, 1917.

first sacral nerve, and the N. pelvicus supplies the descending colon, rectum, anus, bladder and genital organs.

The Enteric System.—The enteric system, which controls the autonomic movements of the hollow viscera, receives fibers from both the sympathetic and the parasympathetic systems, but is not yet sufficiently marked to consider it as an independent system.

AUTONOMIC DRUGS.

I. The drugs which act especially on the autonomic system are the atropin group, the pilocarpin, eserin groups and choline. *These drugs act especially on the parasympathetic system.*

II. The epinephrin group of drugs, which act on the *sympathetic.*

III. The nicotin group, which acts especially on the ganglion cells and *acts on all ganglion cells of both systems.*

IV. Morphin acts on the enteric system. The action is peripheral on Auerbach's plexus. This is the only undoubted peripheral action of morphin.

The chief actions of atropin are: Paralysis of the parasympathetic nerve-endings, with consequent—

Dilation of the pupil.
Rapid heart.
Xerostomia due to suppression of the saliva.
Anhydrotic action.
Suppression of the mucous secretion.
Diminution of the gastric and the intestinal secretions.
Suppression of excessive peristalsis.
Antagonistic action to eserin, pilocarpin, etc.

ATROPIN AND PILOCARPIN GROUP.

Experiment I.—Take a normal dog, count the pulse and respiration and note the size of the pupil and the flow of the saliva. Give him a hypodermic injection of 0.5 c.c. of 1 per cent. pilocarpin nitrate. Note the effect on respiration, heart-rate, pupils and salivary flow. When a marked flow of saliva has been obtained, inject 1 c.c. of 0.1 per cent. atropin sulphate and make observations again.

Experiment II.—This experiment may be done only when it is desirable to study the mechanism of atropin action. Anesthetize a dog, cat or rabbit and prepare for blood-pressure and respiratory tracing and for vagus stimulation. Insert a cannula in Wharton's duct and isolate the chorda tympani and prepare for stimulating it.

PLATE VI

BELLADONNA.

Leaves and root of Atropa B. The alkaloid Atropine represents the drug fully.

Classified as:

Cerebral stimulant.	Deliriant narcotic.	Mydriatic.
Cardiac stimulant.	Anodyne.	Antihidrotic.

Physiologic action:

In general, "atropine acts as a stimulant to the central nervous system and paralyzes the terminations of a number of the nerves, more especially of those that supply involuntary muscle, secretory glands and the heart." [CUSHNY.] It paralyzes peripheral inhibition. It decreases the secretions generally, except the urine, and increases the body temperature, producing a condition simulating fever.

Nervous System.

Brain. Stimulates the cerebrum, especially in its motor areas.

Medulla. Stimulates respiratory and vasomotor centers.

Spinal cord. Depresses inhibitory centers.

Nerves.

Sensory. Depresses sensory nerve endings.

Motor. Depresses motor nerves.

Secretory. Paralyzes the endings of many of the secretory nerves, causing a diminution or arrest of the secretion; hence there result dryness of the mouth, lessened secretion of gastric and pancreatic juices and of milk. The sweat glands are rendered less active.

Vagus. Paralyzes the inhibitory terminations of the vagus within the heart, and the secretory terminations within the digestive system.

Muscular System. Depresses unstriped muscle, but has no influence upon voluntary muscle. Lessens the movements of stomach, intestines, bladder, uterus, and in general the organs containing unstriped muscle, except the arterial walls. [CUSHNY.]

Eye. Pupils are dilated by paralysis of terminals of the motor oculi nerve in the iris, with possible stimulation of the sympathetic terminals. It paralyzes accommodation. Most authorities state that it increases intraocular pressure.

Circulation. Arterial pressure is increased, chiefly by central vasomotor stimulation.

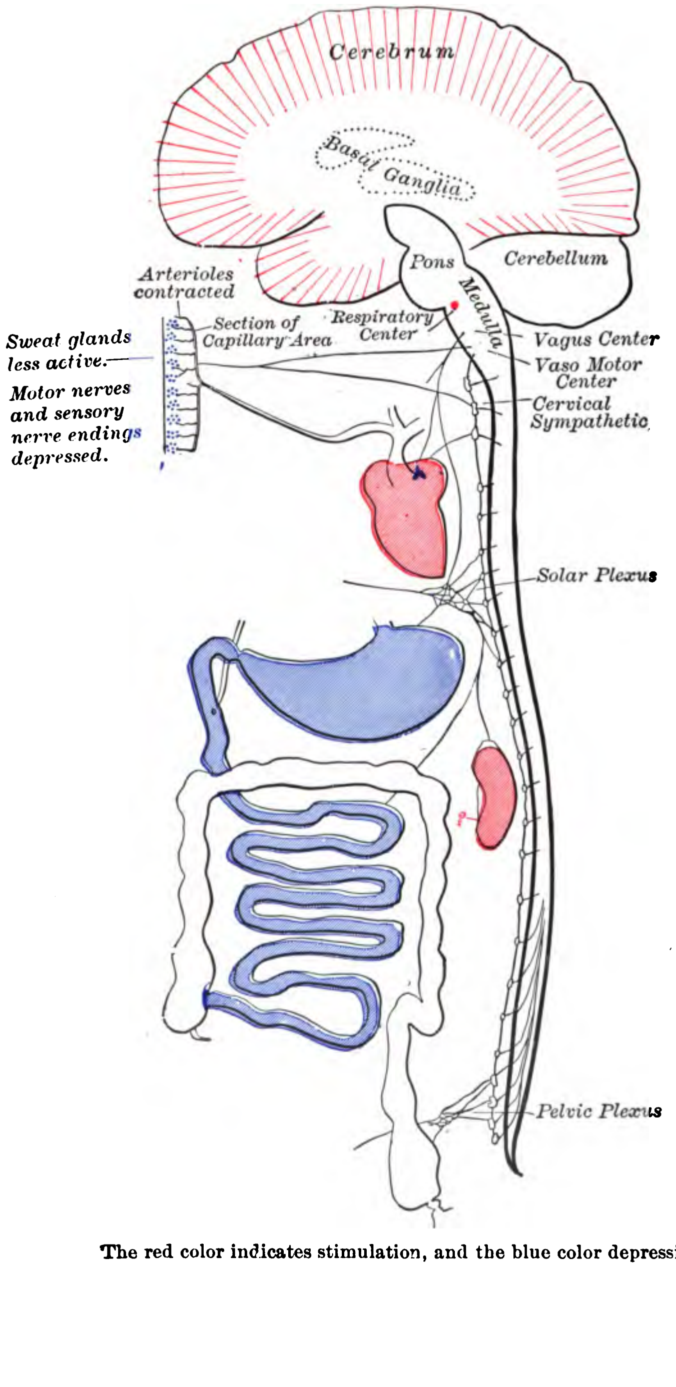
Heart. Increases pulse rate by paralyzing inhibition (peripheral ends of vagus). The heart muscle or its accelerator nerves may feebly be stimulated.

Capillary area. Arterioles are contracted.

Respiration. Stimulated by action upon respiratory center.

Excretion. Perspiration is lessened. The drug is excreted rapidly by the kidneys, but its influence upon their activity is uncertain.

PLATE VI



The red color indicates stimulation, and the blue color depression.

1. Take normal tracings.
2. Stimulate the chorda tympani; stimulate the vagus.
3. Stimulate both simultaneously.
4. Inject 0.5 c.c. pilocarpin nitrate intravenously. Note results in the eye, saliva, heart, respiration and blood-pressure. Stimulate the chorda and vagus separately. Inject 0.5 c.c. of 1 per cent. atropin sulphate and repeat stimulations.

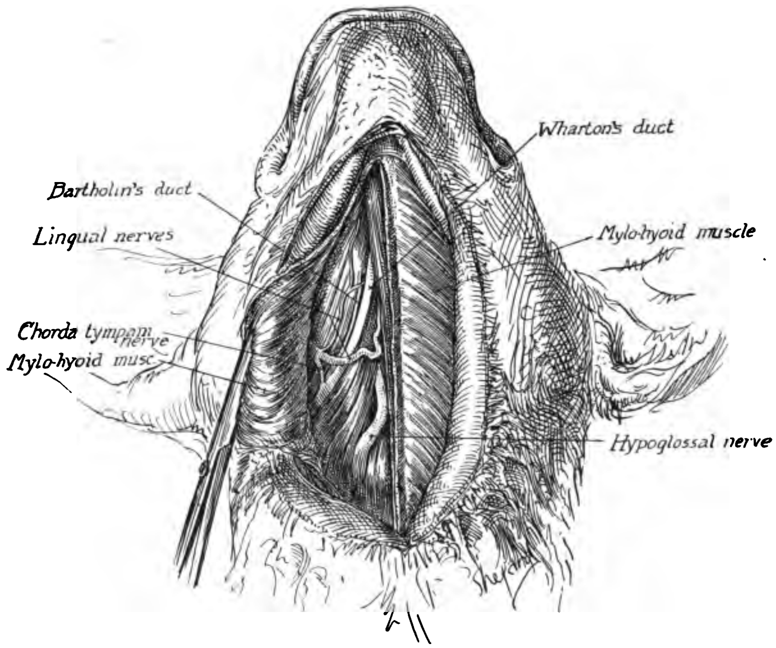


FIG. 35.—Dissection to show region of Wharton's duct. The lingual and chorda tympani nerves are sometimes called the chorda linguæ in descriptions.

5. When stimulation of the chorda gives no saliva, place the electrodes in the hilus of the gland and stimulate. Stimulation of the sympathetics, either with the electrodes or with adrenalin, still causes a flow of saliva, hence the gland cells are not paralyzed. The action, therefore, is not on the gland cells. Either isolate and stimulate the cervical sympathetic, peripheral to the superior cervical ganglion or give the animal 1 c.c. of 1 to 10,000 epinephrin and note the results on the saliva.

Experiment III.—*Effect of Atropin on the Eye.*—Take a number of animals—dog, cat, rabbit, guinea-pig, chicken or pigeon—and drop 1 per cent. atropin sulphate in one eye and 1 per cent. eserin in the

other. Record the action. Take a frog, pith and remove the eyes. Place one in a solution of 1 per cent. atropin and the other in a solution of 1 per cent. pilocarpin or eserin; set in a dark place. Why in a dark place? Compare and record the results on all animals.

Experiment IV.—*Action of Atropin on the Frog and Turtle Heart.*—1. Take a frog and turtle and isolate the heart and vagus. Take a tracing by the suspension method. Stimulate the vagus. Now apply 1 per cent. pilocarpin and again stimulate the vagus. Repeat this several times.

2. Apply 1 per cent. atropin and again stimulate the vagus. When the vagus stimulation is ineffective, again apply pilocarpin. What is the result? Discuss the antagonism of atropin and pilocarpin.

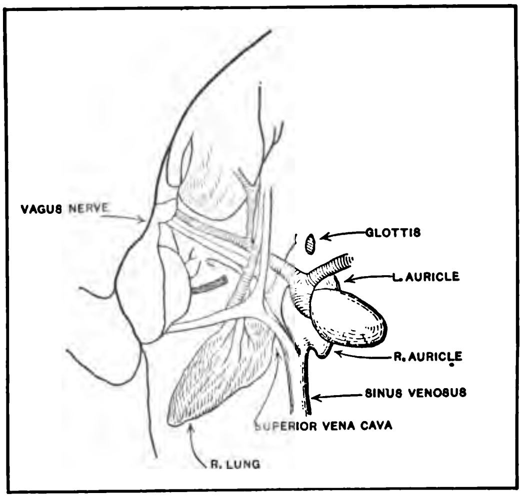


FIG. 36.—Relation of the vagus nerve in the frog as modified from Schäfer.

Experiment V.—*Action of Pilocarpin and Atropin on Turtle Heart Strips.*—Set up heart strips in saline in the usual way. When the contractions are regular add a 1 per cent. solution of pilocarpin nitrate in saline until the bath around the strip is 0.1 per cent. of pilocarpin. After thirty minutes, or when good records are obtained, replace the bath with normal saline.

When contractions are again regular, add 1 per cent. atropin in successive amounts until the bath contains 0.001, 0.01 and 0.1 per cent. atropin sulphate.

Experiment VI.—Repeat Experiment V, using the atropin before the pilocarpin.

Experiment VII.—Use physostigmin salicylate instead of pilocarpin nitrate (*a*) before atropin and (*b*) following atropin.

Experiment VIII.—*Effect of Atropin and Pilocarpin on the Volume of the Respired Air.*—1. This experiment may be carried out in connection with some of the previous experiments; anesthetize the animal and arrange for blood-pressure and respiration tracings. Take the respiration tracing from a band around the chest or abdomen. Insert a tracheal cannula for connection with a spirometer. Take normal tracing and measure the volume of expired air per minute and the rate of respiration.

2. Inject slowly 1 c.c. of 0.5 per cent. pilocarpin nitrate intravenously and note change in blood-pressure, heart-rate, respiration-rate and volume. Repeat injection if necessary. After fifteen minutes, measure the respiratory volume and inject slowly 0.1 per cent. physostigmin until the first effect of the blood-pressure is noticed. Measure the respiratory volume again.

3. Now inject 1 c.c. of 0.5 per cent. atropin sulphate and record the influence on the heart and respiration. Repeat if necessary.

Experiment IX.—*Action of Pilocarpin, Physostigmin and Atropin on Uterine Strips.*—Remove the uterus from a guinea-pig, cat or rabbit and place it in warm saline and keep a current of air or oxygen running through the saline. Mount a small piece of it in warm saline and take a record of the contractions. When contractions are regular add pilocarpin until the solution contains 0.01 per cent. then 0.1 per cent. What is the result? Now change the saline and when contractions are regular add 0.001 per cent. atropin sulphate, 0.01 and 0.1 per cent. and note results.

Experiment X.—Repeat Experiment IX, using atropin first.

Experiment XI.—Repeat Experiment IX, using physostigmin 0.01 and 0.1 per cent. instead of pilocarpin.

Experiment XII.—*Action of Atropin and Physostigmin on the Intestinal Movement.*—From the animal used in the previous experiments, carefully remove rings of the small intestine and take tracings as with uterine strips. To obtain the best contractions an adequate weight must be applied. The best condition can only be obtained by experimenting. Use the same drugs as in the uterine strips.

Experiment XIII.—Use a dog that has been one day without food. Insert a tracheal cannula and attach to an ether bottle.

1. Pith the dorsal spinal cord in the following manner: Cut down to the laminæ of the first and second lumbar vertebræ, detaching the muscles from the spinous processes. With bone forceps remove

these processes and the laminæ (controlling hemorrhages with pledgets of cotton saturated with ferric sulphate solution, 5 per cent.), exposing the spinal cord. With rotary motion insert anteriorly a soft wire with the end recurved to form an open hook about 4 or 5 mm. across. Remove the wire. Insert a cotton pledget and close the incision (see Fig. 17).

2. Prepare the gut for tracings as described under epinephrin. Experiment IV (2) (page 167).

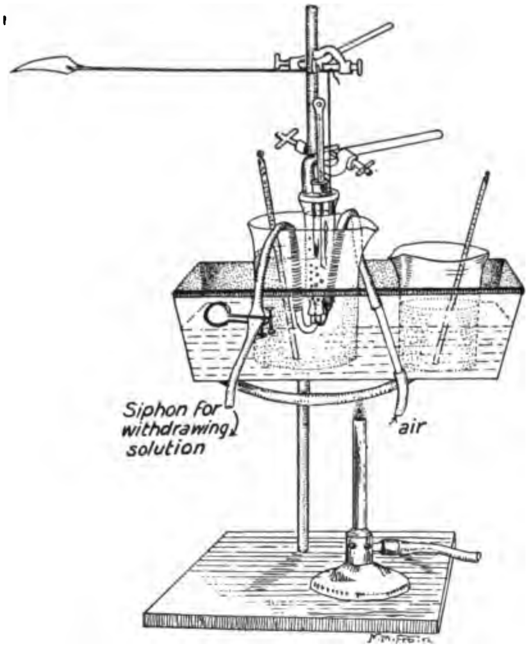


FIG. 37.—Apparatus for recording contractions of uterine or intestinal strips. The air is supplied through a hypodermic needle. Instead of the siphon a vessel may be prepared, where the outlets can be made directly through the vessel wall.

3. Arrange for injections into the femoral vein with a burette. Take preliminary control tracings, one complete revolution, showing at the beginning the effect of (1) lifting gut; (2) inserting a needle into the gut; (3) replacing the gut and at another place the introduction of Ringer's solution into the abdominal cavity at body temperature. Note the effects of respiration on the curve. Then note the effects of the following procedures:

1. Injection of 20 c.c. of 5 per cent. NaCl solution into the lumen of the gut (one revolution).
2. Intravenous injection of pilocarpin solution, 1 c.c. of 1 to 1000.
3. Intravenous injection of 5 c.c. of 0.5 per cent. atropin sulphate.

Experiment XIV.—*Antagonism of Atropin to Morphin.*—1. Take the normal respiration and heart-rate of a dog. Note the condition of the pupil. Give him a hypodermic of 1 c.c. of 3 per cent. morphin sulphate. After thirty minutes repeat the records.

2. Give an intravenous injection or a hypodermic of atropin sulphate, 1 c.c. of 0.5 per cent., and again make records. If the animal is much depressed from the morphin give the atropin intravenously.

Experiment XV.—Students will divide into groups. Count the heart and the respiratory rate. Note the size of the pupil, condition of skin, reflexes, etc.

Group I. Each pupil take $\frac{1}{6}$ grain (0.01 gram of pilocarpin.)
II. $\frac{1}{3}$ grain, 0.02 gram.
III. $\frac{1}{2}$ grain, 0.03 gram.

Observe as above until sweating commences. If sweating is excessive take $\frac{1}{100}$ grain of atropin every fifteen minutes until sweating is arrested. Do not take more than two doses of the atropin unless sweating is excessive.

Groups IV, V and VI. Take $\frac{1}{100}$ grain of atropin first, then after fifteen minutes take the amount of pilocarpin used by Groups I, II and III.

NICOTIN.

Nicotin, like curara, is an important drug in research work and in illustrating selective action. Because of the widespread use of tobacco the action of nicotin is important from an economic point of view. It is also a violent poison. Its first action is on the ganglion cells. All ganglion cells, sympathetic and parasympathetic, are acted upon.

Experiment I.—To show the selective action of nicotin on the ganglion cells: Anesthetize a rabbit, cat or dog and dissect the cervical sympathetic and lay bare the superior cervical ganglion. Stimulate the nerve below, on, and peripheral to the ganglion. Note the dilation of the pupil and the constriction of the ear vessels. Paint the nerve below the ganglion with 1 per cent. nicotin. Stimulation over this painted area or below it shows no block of the impulse. Now paint the ganglion. In a few minutes stimulation below or on the ganglion shows that the impulses are blocked while stimulation peripheral to the ganglion still gives dilation of the pupil and dilation of the ear vessels. If the animal is in condition, prepare for blood-pressure and respiration as in Experiment II.

Experiment II.—Prepare a dog or rabbit for blood-pressure and respiration tracings and for stimulation of the vagus.

1. Inject intravenously 1 c.c. of 1 to 10,000 epinephrin. Note results on heart-rate, blood-pressure and respiration.
2. Stimulate the vagus again.
3. Inject 5 c.c. of 0.1 per cent. nicotin solution and note the effect on the heart-rate, blood-pressure and respiration.

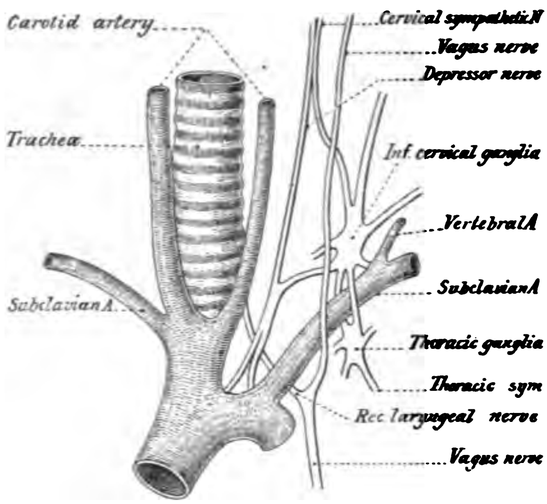


FIG. 38.—Diagram of inferior cervical and thoracic ganglia in the rabbit. (After Foster.)

4. Stimulate the vagus again. If it is still active repeat the injection of nicotin.
5. Inject 1 c.c. of 1 per cent. pilocarpin nitrate and note effect as before.
6. Stimulate the vagus again.
7. Inject 5 c.c. of 0.1 per cent. nicotin solution again in five minutes.
8. Inject 1 c.c. of 1 per cent. atropin sulphate and note the influence on the heart-rate, blood-pressure and respiration.
9. Stimulate the vagus again.
10. Inject 5 c.c. of 0.1 per cent. nicotin solution and compare the effect with previous injections.
11. Inject 1 c.c. of 1 to 10,000 epinephrin. Discuss results.

Experiment III.—Inject 1 c.c. of 0.1 per cent. nicotin into the lymph sac of a frog. Note and make diagrams of the position of the animal from time to time. Note the twitchings of the muscles. What is

the influence of cutting the sciatic on the twitchings? Stimulate the peripheral end of the sciatic.

2. Compare this action on the muscles with that of another frog in which one injects 1 c.c. of 1 per cent. physostigmin. Twitchings of the muscles should develop in this animal, too, but they do not stop when the nerve is cut. Curara causes the physostigmin twitchings to stop. Strong $MgSO_4$ also causes them to stop.

Experiment IV.—*Demonstration; Nicotin in Tobacco Smoke.*— The main active ingredient of tobacco smoke is nicotin. To show the nicotin-like action of tobacco smoke, place a couple of frogs in a large bottle or under a bell-jar and insert a two-holed stopper in the vessel used. In one hole place a pipe or thistle tube containing tobacco. In the other place a glass tube reaching to the bottom of the vessel. Attach a rubber tube to the glass tube and light the tobacco. Aspirate the smoke into the bottle and notice the influence on the frogs. Compare these animals with those that got pure nicotin.

Experiment V.—Place one drop of nicotin on the tongue of a mouse, guinea-pig or other small animal and notice effect.

Experiment VI.—Count the respiration and heart-beat and note the size of the pupil and the salivary flow in a dog. Give intravenously, without an anesthetic, 5 c.c. of 0.01 per cent. nicotin and note the changes. Repeat injection of nicotin if necessary.

Experiment VII.—Anesthetize a dog and inject 0.5 c.c. of 0.1 per cent. nicotin into the lumbar cord. Note the result on the reflexes.

Experiment VIII.—The influence of nicotin in modifying the tracing of epinephrin. Take the blood-pressure in a dog in the usual way. Inject 0.5 c.c. of 1 to 10,000 epinephrin into the femoral vein. When the pressure returns to normal give 0.025 c.c. of 1 per cent nicotin solution and record the effect on the blood-pressure. Alternate the epinephrin and nicotin injections until definite results are obtained. After a time nicotin gives no rise of blood-pressure, but epinephrin is still effective. How do you explain these actions?

NOTE.—See Epinephrin, page 166, which should be included in autonomic drugs.

CHAPTER XIII.

PHARMACOLOGY OF THE EYE.

Function.—Vision.

Essential Organ.—The retina and optic nerve.

Accessory Organs.—The internal and external muscles, lacrimal glands, lens, etc.

The retinal ganglionic layer may be considered similar to the spinal sensory ganglion cells. The peripheral parts being receptive endings and the optic nerve the continuation centralward of the afferent nerve.

These facts explain why methyl alcohol, quinin, santonin, tobacco, male fern, alcohol, pelletierin, carbon bisulphide, napthols, etc., which injure the retinal ganglion cells may also injure the optic nerve.

Drugs Acting on the Lacrimal Glands.—The atropin group causes a lessened secretion of tears.

The pilocarpin group stimulates.

In eye work when these drugs are used the drying effect of atropin is not a serious drawback in the use of the drug. After large doses of pilocarpin the tears are markedly stimulated. However, moistening of the eyeball is not due entirely to the lacrimal glands because after their removal or disintegration the eye does not become dry. The secretion of the conjunctiva itself and its mucous glands aid in the moistening of the eye.

The nerves to the lacrimal glands are the lacrimal, a branch of the ophthalmic nerve, which in turn is one of the three primary divisions of the fifth nerve, a parasympathetic nerve.

Drugs Stimulating the Retinal Cells or Vision.—Strychnin increases the acuteness and also enlarges the field of vision.[1]

The caffein group of drugs have a similar action.

Drugs Depressing the Retinal Function.—Drugs are not known that definitely reduce the retinal hyperesthesia with severe pain. Pain arising from the conjunctiva may be reduced by the local application of cocain and by the central action of the alcoholic group or morphin.

[1] Filenhe: Pflüger's Archives, 1901, vol. iii.

The Iris and the Ciliary Muscle.—The function of these is to constrict and enlarge the pupil, hence to regulate the amount of light that reaches the retina (see Fig. 19, page 99). The iris consists of two sets of muscle fibers: (1) circular and (2) radiating.

Stimulation of the constrictor fibers narrows the pupil. The third nerve governs the action of the circular muscle fibers while the sympathetic system governs the radiating.

Any of the drugs acting on smooth muscle would act on the muscles of the eye if applied directly; practically, however, direct muscular action is unimportant. The important action is due to an action on the nerves.

Drugs Stimulating the Third Nerve (Parasympathetic Endings).—(1) Eserin and (2) pilocarpin.

Drugs Paralyzing the Third Nerve Endings.—(1) Atropin and (2) substitutes.

Drugs Stimulating the Sympathetic Nerves to Radiating Fibers.—(1) Epinephrin and (2) cocain.

Drugs Paralyzing the Sympathetic Nerve Endings in the Eye.—(1) Cocain in large amounts paralyzes all nerve endings. Ergotoxin will paralyze the constrictors. However these actions are not especially prominent in the eye and are perhaps little in operation here.

Drugs Changing the Size of the Pupil by a Central Action.—1. Morphin, pin-point pupil.

2. Chloral, pin-point pupil.

3. Asphyxia, first constricts then dilates.

4. Drugs causing dilation due to paralysis of the central end of the third nerve—certain ptomains, for example, fish, muscles, cheese, sausage, etc.

Proof that Atropin Dilates the Pupil by Paralysis of the Third Nerve Endings.—1. The action is peripheral because when applied to the eye locally and the drug is kept from being absorbed it dilates the pupil.

2. It will dilate the pupil after degeneration of the sympathetic nerve.

3. The action is peripheral, since it acts on the enucleated eye.

4. Stimulation of the third nerve peripheral to the ganglion is not effective after atropin, though active before. Direct stimulation of the muscle in such cases is effective.

5. Atropin antagonizes the action of eserin and pilocarpin.

6. Atropin has no action on the sympathetic nerves to the eye.

7. It is not known to have any action on the muscles of the eye.

Proof that Eserin and Pilocarpin Stimulate the Third Nerve Endings. —1. They act on the enucleated eye, therefore the action is peripheral.

2. Stimulation of the sympathetic peripheral to the superior cervical ganglion is still effective after these drugs, therefore the action is not due to a paralysis of the sympathetic.

3. The action does not occur after degeneration of the nerves, therefore it is not on the muscle.

4. Direct stimulation of the muscle still produces contraction.

5. The opinion that the action is on the nerve-endings of the third nerve is corroborated by the action on other locations innervated by the parasympathetics.

Some Differences in the Action of Eserin and Pilocarpin.—The chief differences in the action of eserin and pilocarpin are:

1. Pilocarpin actually stimulates the nerve-endings while eserin merely sensitizes the endings and renders them very responsive to stimuli, reaching them from the nerve. The basis for this belief is: If the chorda tympani nerve be cut, eserin often fails to cause secretion while pilocarpin causes secretion.

2. Eserin injected into Wharton's duct to reach the endings directly will cause no secretion if impulses from the center are blocked while pilocarpin causes secretion.

3. Eserin likewise fails to contract the pupil after degeneration of the postciliary branches, while pilocarpin is still effective.

CHAPTER XIV.

ANTAGONISM.

By antagonism we mean counteraction of the effects of one drug by another: It may be one of two kinds:

I. Chemical.

II. Physiological.

Chemical antagonism is easily understood in most cases. When gastric hyperacidity is neutralized by sodium bicarbonate or when the action due to the intravenous injection of an acid is neutralized by a similar injection of sodium bicarbonate the explanation is apparent. Some writers call this chemical antagonism, distoxication or neutralization, and reserve the term antagonism to physiological actions.

PHYSIOLOGICAL ANTAGONISM.

The classic example of antagonism is atropin and pilocarpin. So far as we know these drugs have no chemical affinity for each other; both are alkaloids, yet they produce exactly opposite effects on the eye, salivary glands, heart, intestine, etc.

The antagonism in this case, as in most cases, is not mutual, *i. e.*, the action of one drug is not equal and opposite to the action of the other. Small doses of atropin will counteract the effects of large doses of pilocarpin, but pilocarpin is not antagonistic to large doses of atropin. In this as in most cases the paralyzing drug is much stronger than the stimulating drug.

The antagonism may be explained in this case by assuming that these drugs act on the same place: the myoneural junctions, one stimulating, the other depressing. When the ending is paralyzed by atropin, of course, no further action can be expected, since paralysis requires a period of recuperation before the ending is again responsive to any stimulus.

On striped muscle, curara paralyzes the nerve-endings; eserin here is antagonistic, but the degree of the antagonism is again limited. The effect of curara soon wears off, but eserin facilitates the recuperation and actually stimulates the endings.

In the case of veratrin, which acts directly on muscle and stimulates it, potassium chloride and fatigue products are antagonistic, and again the paralyzing drugs are stronger than the stimulating.

Barium and the nitrites are antagonistic on muscle, but we do not know whether they act on the same substance in the muscle.

Barium, veratrin and digitalis increase the force of contraction of the heart while chloroform, chloral and potassium salts diminish it. In this and in many other cases of antagonism it is difficult to analyze the mechanism because there are so many possible factors. It is not at all necessary that antagonistic drugs act on the same point, since the reciprocal nerves in many organs are antagonistic in their physiological effect, as has already been pointed out.

HCN, CH_3, CN, and other nitrils, in the presence of active sulphur compounds, are converted into less toxic sulphocyanides. They also retard or modify the power of the body to break down substances which in themselves are not toxic, yet their decomposition products are toxic. Hunt's acetonitril test illustrates this type of antagonism.

Hunt found that the administration of thyroid gland extract to white mice for a few days markedly increases their resistance to an acetonitril. He found that after thyroid feeding, acetonitril, which is toxic, by being broken into HCN is less toxic after feeding thyroid. Certain foods, not well understood, may have a similar influence, since dextrose, oatmeal, liver and kidney also increase this antagonism.

Little is known regarding this type of antagonism or the antagonism resulting from internal secretions or hormones.

Epinephrin sensitizes sympathetic nerve-endings. Cholin is thought to sensitize autonomic ganglia. The chemical functions of the liver are modified by the amount of epinephrin in the blood and also by the condition of the thyroid. Modifications of these and other functions undoubtedly synergize or antagonize drug action, but too little is known about such action to give an explanation.

Disease, climate, food and perhaps other conditions may antagonize morphin. In cold climates purgatives are less effective than in warm. Many other unknown conditions may modify the action of drugs.

Synergism.—Synergism is the opposite of antagonism. The term is confused with additive action. In true synergism the sum of the influence of two drugs is more than the addition reaction of the two. There is a sensitizing action by one of them, so that the other produces more than its normal action. For example:

1. A mixture of purgatives increases the activity of both.
2. Morphin and chloral and
3. Morphin and scopolamin as hypnotics.
4. Mercury and arsenic in syphilis.

No explanation of synergism is at present available.

Scopolamin, Morphin, Synergism.[1]—In the following experiments record respiration and heart-rate, corneal reflex and general appearance and condition of animals before and during the experiment.

Experiment I.—Give a rabbit 0.03 gram of morphin per kilo subcutaneously and observe and record the effect for one hour.

Experiment II.—Give a rabbit 0.02 gram per kilo (1 c.c. of 2 per cent.) scopolamin subcutaneously and observe and record the effect for one hour.

Experiment III.—Give a rabbit 0.04 gram of morphin per kilo (1 c.c., 4 per cent.) subcutaneously and observe and record the effect for one hour.

Experiment IV.—Give a rabbit 0.03 gram of morphin per kilo (1 c.c., 3 per cent.) and 0.01 gram per kilo (1 c.c., 1 per cent.) scopolamin and observe and record the effect for one hour. Compare the results of these four experiments.

Experiment V.—Give a rabbit 0.01 gram of morphin and 0.01 gram of scopolamin (1 c.c., 1 per cent.) per kilo and observe for one hour.

Experiment VI.—Select two cats the same size. (*a*) Give one as a control 0.05 gram of morphin (1 c.c., 5 per cent. or equivalent) and notice the effect after thirty minutes.

(*b*) Give the second animal 0.100 gram of narcotin subcutaneously. Note the influence of this for one hour. Then give the same amount of morphin (0.05 gram) as the control and observe for one hour.

(*c*) Take A and after one and a half hours give the same dose of narcotin as B (0.100 gram) and compare the two animals.[2]

Experiment VII.—*Synergism of Morphin and Papaverin.*—Repeat Experiment VI, using papaverin instead of narcotin.

Experiment VIII. — *Synergism of Morphin, Scopolamin and Atropin.*—Take five cats. Inject three cats each with 25 mg. per kilo of morphin subcutaneously.

1. Use as a control.

2. Give the second animal 1 c.c. of 0.1 per cent. scopolamin hypodermically.

[1] Madelung: Arch. of Exp. Path. u. Pharm., 1910, lxii, 422.
[2] Straub: Biochemische Ztschr., 1912, xli, 459.

3. Give this animal 1 c.c. of 0.01 per cent. atropin.
4. Give 1 c.c. of 0.1 per cent. scopolamin as control.
5. Give 1 c.c. of 0.1 per cent. atropin as control.

Compare and record results.

Scopolamin and urethane are also synergistic,[1] also morphin and urethane. The narcotic dose of urethane for a rabbit is 1.5 gram per kilo by mouth or 1 gram per kilo subcutaneously.

Experiment IX.—Give two rabbits each 0.1 gram per kilo of scopolamin subcutaneously. Save one for control. Give the other 0.2 gram per kilo urethane subcutaneously. To a third give 1 gram per kilo urethane by stomach tube.

Experiment X.—Give two rabbits 0.2 gram per kilo of urethane subcutaneously. Save one for control. Give the other 0.1 gram per kilo of scopolamin. Compare the results of this in both experiments.

In the same way Burgi has found that the antipyretics have some anesthetic action and increase the action of morphin and urethane.

EXAMINE AND STUDY THE VARIOUS PREPARATIONS IN WHICH EPINEPHRIN IS FOUND IN THE MARKET.

Experiment I.—1. Prepare a dog or cat for blood-pressure and respiration tracings. Note the condition of the pupil before and after each injection. Insert a cannula into the femoral vein for intravenous injections from a burette. Make an incision along the linea alba, about four inches long, and observe the condition of the intestine during each injection. Keep the part warm and closed when not under observation. Take three samples of the blood and determine clotting time.

2. Take normal tracings, then tracings of the action of 1 c.c. of 1 to 10,000 epinephrin subcutaneously.

3. After five minutes inject 1 to 50,000 epinephrin intravenously; when pressure is high stimulate the vagus, compare with stimulation when the pressure is normal.

4. Isolate and cut one vagus and again inject 1 to 10,000 epinephrin.

5. Isolate and cut the other vagus and inject 1 to 10,000 epinephrin. Is there any change in the height or character of the curve after cutting the vagi? Is there a secondary rise in the pressure following a primary fall? If so how do you explain it?

[1] Burgi: Deut. Med. Wchschr., 1910, pp. 20 and 62.

6. When the pressure is again normal, stimulate the peripheral vagus.

7. Take the clotting time of the blood and compare with the normal.

8. Inject intravenously 2 c.c. of pituitrin (liquor hypophysis), 1 to 5 in water. Compare this action with the action of epinephrin.

9. When the pressure is again normal inject double the amount of pituitrin (liquor hypophysis) subcutaneously. Note effects for thirty minutes.

10. At this stage inject 1 c.c. of 1 per cent. atropin sulphate solution. What is the effect on the heart, respiration and eye? Study the changes in the tracings under the various drugs.

Experiment II.—Prepare for tracings as in Experiment I. Watch the effects on the pupils, heart, respiration, intestine and salivary flow. Determine the clotting time of the blood.

1. Inject 2 c.c. of 1 to 5 solution of pituitrin (liquor hypophysis) intravenously. Wait until the pressure has returned to normal. Determine clotting time. Then—

2. Inject 1 c.c. of 1 to 10,000 epinephrin. When pressure is again normal—

3. Inject 1 c.c. of 1 per cent. atropin sulphate, in five minutes—

4. Inject 1 c.c. of 1 to 10,000 epinephrin and compare the result with 2 to 5, Experiment I. Determine clotting time again.

5. Expose the intestines to produce a condition of shock and when the blood-pressure has been much reduced, again inject 1 c.c. of 1 to 10,000 epinephrin.

Experiment III.—*Action of Epinephrin on Vasodilators.*—Prepare for tracings as in Experiment I and II.

1. Take normal tracing.

2. Inject intravenously $\frac{1}{4}$ c.c. per kilo of 1 to 100,000 epinephrin solution. Repeat this and vary the dose and see if you can get a dose that will give a fall only. Note that a slight rise may be followed by a fall and again by a secondary rise. How do you account for this?

3. Inject slowly $\frac{1}{10}$ c.c. per kilo of the fluidextract of ergot.

4. Repeat (2).

5. Repeat (3).

6. Repeat (2).

Instead of ergot, ergotoxin may be used if it is available. Prepare a solution of ergotoxin as follows: Weigh out 0.1 gram and place in a beaker. Moisten with 10 per cent. NaOH. Add water slowly, and about 1 c.c. at a time, until the powder is dissolved. Make

to 20 c.c. This is 0.5 per cent., and 1 c.c. equals 0.005 gram. Ergotoxin paralyzes the vasoconstrictors before the dilators.

Experiment IV.—*The Action of Epinephrin on the Intestine.*—Anesthetize the animal and prepare for recording the intestinal movements by the Trendelenburg method or by Jackson's finger-cot method.

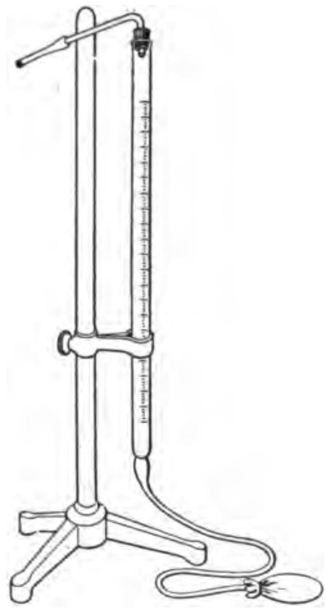


FIG. 39.—Jackson's finger-cot method of recording intestinal contraction.

1. Trendelenburg's method as described by Dr. R. G. Hoskins: Use a dog that has been one day without food. Insert a tracheal cannula and attach to an ether bottle (see Fig. 17, page 86.)

Pith the Dorsal Spinal Cord in the Following Manner: Cut down to the laminæ of the first and second lumbar vertebræ, detaching the muscles from the spinous processes. With bone forceps remove these processes and laminæ (controlling hemorrhages with pledgets of cotton saturated with ferric sulphate solution, 5 per cent.), exposing the spinal cord. With rotary motion insert anteriorly a soft wire, with the end recurved, to form an open hook about 4 or 5 mm. across. Remove the wire. Insert a cotton pledget and close the incision.

2. *Prepare gut for tracing* as follows: Make an opening in the abdominal wall along the linea alba and sew in an iron ring

about 14 cm. in diameter. Fasten the ring to a stand and fill the abdominal cavity with Ringer's solution at body temperature. *Avoid all rough handling.* Pass a guide ligature around the gut (to be used for drawing the gut up when injections are to be made into it); and 25 to 30 cm. below it, by means of a small surgical needle pass a silk thread, fifteen inches long, in a transverse direction through the superficial layer of the gut, and after tying pass the end through the glass cylinder (finger plethysmograph). One-half inch above this thread sew a single superficial stitch. Sew the opposite end of the cylinder to the gut a half-inch below in the same way. Fix the cylinder perpendicularly in a burette clamp and attach the long thread to a heart lever arranged to magnify seven times and to write on a kymograph drum. (The cylinder decreases the displacement of the gut respiratory movements.)

3. Arrange for injections into the femoral vein from a burette. It usually requires thirty to sixty minutes for good contractions to commence.

Experiment V.—*Jackson's Finger-cot Method.*—Arrange a burette, catheter and finger-cot or rubber glove finger as shown (Fig. 39), and make a small longitudinal incision in a loop of the small intestine. Slip the end of the catheter over which the finger cot is attached about four or five inches down the lumen of the intestine from the incision. (The tip of the catheter reaches entirely to the end of the finger cot and thus forces the cot along.) Fill the burette half-full of water and move the catheter in and out a little to be sure that the finger cot is filled with water and the air is expelled. Stitch together the incision in the intestine around the catheter and close the abdomen with hemostats. The intestinal tambour should write just above the blood-pressure, respiration and base line.

Experiment VI.—*Action of Epinephrin on the Uterus.*—(*a*) Remove the uterus of a guinea-pig, rabbit or cat. Place in a warm saline solution. Take a piece of one horn, about one-half inch long, and set up as for muscle contractions in a warm saline bath (Fig. 37). Keep oxygen or air bubbling through the immersing fluid. When contractions are regular add a drop or two of 1 to 1000 epinephrin solution.

(*b*) Remove and add saline again. When contractions are again regular add 1 c.c. of 1 to 10 pituitrin.

(*c*) Remove the pituitrin fluid and physiological saline. When contractions are regular add

(*d*) 1 c.c. of 1 to 10 fluidextract of ergot. Other drugs may be tried as desired.

Experiment VII.—*Barbour's Method of Studying the Action of Drugs on the Uterus.*[1]—Get this journal and read the article. Barbour's method of recording uterine contractions is much like the Trendelenburg method for intestinal movements. An opening is made in the linea alba and the horns of the uterus loosened and brought forward together and a thread tied around the ends of both. Now place a glass tube, like a finger plethysmograph, perpendicular in the abdomen, so that it contains the uterus and protects it from the other abdominal organs. Bring the thread that is around the uterine horns through the tube and attach to a light writing lever. Fill the abdomen with liquid paraffin for protection and sew the skin of the abdomen around the tube. Inject the drugs to be studied into the femoral vein. This method should give a more accurate indication of drugs on the uterus than a method that applies the drugs directly to the uterus, a form in which they never reach it when given therapeutically. Cats are the best animals for this work.

Experiment VIII.—*The Action on the Eye.*—(*a*) The eye should have been observed in all the foregoing experiments.

(*b*) Take the eyes of a frog and place them, one in saline, 0.8 per cent., the other in saline containing 1 to 10,000 epinephrin. Place in a dark place and observe every fifteen minutes. What is the result? Why does this occur in the dark more easily than in daylight?

Experiment IX.—*The Action of Epinephrin on the Secretions.*—(*a*) Anesthetize a dog and place a cannula in Wharton's duct and prepare for blood-pressure tracings, stimulation of the chorda tympanum and cervical sympathetics. Take normal tracing and record of blood-pressure and salivary flow. Stimulate the chorda and sympathetic separately. Note the results. If the sympathetic cannot be conveniently isolated proceed without it.

(*b*) Inject 1 c.c. of 1 to 10,000 epinephrin and note the effect on the salivary flow. Repeat.

(*c*) Inject epinephrin. When satisfied with the action of epinephrin on the secretion again stimulate the chorda.

(*d*) Inject intravenously 1 c.c. of 1 per cent. atropin sulphate and in five minutes repeat stimulation of the chorda.

(*e*) When the stimulation of the chorda is ineffective repeat injections of epinephrin 1 to 10,000 and note results. If the sympathetics have been isolated stimulate directly.

[1] Journal of Pharm. and Exp. Ther., 1915, vii, 547.

Experiment X.—*Glycosuria Produced by the Hypodermic Injection of Epinephrin.*—Catheterize a rabbit and test the urine for sugar. If there is sugar, inject 1 c.c. per kilo of 1 to 10,000 epinephrin subcutaneously. In two to three hours catheterize and again test the urine for sugar. The test rarely fails.

Experiment XI.—*The Action of Epinephrin on the Tone of Bronchial Muscle.*—The bronchial muscles are acted on by drugs that act on non-striated muscle. They are relaxed by atropin and constricted by drugs of the pilocarpin-eserin group, etc. Elimination of the indirect action of the drug on respiration and vasomotor apparatus makes the measurement of the bronchial tone rather difficult. Care must be taken to avoid an action on the respiratory center being interpreted as an action on the bronchial muscles. For this reason the animal is pithed and artificial respiration is carried out. Changes in the blood flow through the lungs must also be accounted and not confused with bronchial changes. Methods have been developed by Dixon and Brodie,[1] Golla and Symes,[2] and D. E. Jackson.[3] The method is essentially as follows:

Anesthetize a dog and insert a three-way tracheal cannula for artificial respiration. Isolate the carotid arteries and ligate one. With a large needle pass ligatures through all the muscles of the neck close to the vertebra so that the entire return circulation from the head can be shut off. When ready to do this inject 2 c.c. of chloroform into the central end of the carotid. This will kill the brain and has the effect of pithing. Commence artificial respiration at once. This method will kill the animal if enough chloroform reaches the heart. It is important, therefore, that as soon as injections of chloroform are made ligation of the return vessels be made at once.

A safer method of pithing is to open the skull with a trephin and pith with an iron rod. Pack tightly with cotton to avoid hemorrhage. Pithing should be sufficiently low to destroy the respiratory center: The simplest method of pithing is to inject 1 c.c. of $CHCl_3$ into the fourth ventricle. This will also destroy the respiratory centre, so that artificial respiration should be established as soon as the injection is made.[4]

Insert a cannula into the jugular or femoral vein for injection. Shave the chest on one side near the diaphragm and insert a flanged

[1] Jour. Physiol., 1903 xxix, 97.
[2] Jour. Pharmacol., 1914, v, 92.
[3] Ibid., iv and v; also Exper. Pharm. Text-book, 1917.
[4] Jour. of Lab. and Chem. Med., 1919, iv, 491.

cannula into the pleura. The opening or incision around the cannula must be air-tight. A little collodion around the incision will help. Connect with a tambour or water manometer and make a tracing of the pulmonary excursions. Keep the respiration regular. If the blood volume in the lungs remains constant and the artificial respiration is regular an increase or decrease in the excursions of the tambour is assumed to be due to changes in the bronchial muscles. Criticize this assumption.

1. Study the effect of the intravenous injection of 1 c.c. of 1 to 10,000 epinephrin.
2. 1 c.c. of 0.1 per cent. pilocarpin.
3. 1 to 10,000 epinephrin.
4. 1 c.c. of pilocarpin, 1 per cent.
5. 1 c.c. of 0.5 per cent. atropin sulphate.
6. Repeat 1.
7. 1 c.c. of 1 to 5 pituitrin.
8. Before killing the animal inject 1 c.c. of 1 per cent. barium chloride.

Note to student: Criticize the technic and conclusions of this experiment. Wherein may the results not indicate an action on the bronchioles?

CHAPTER XV.

ANTIPYRESIS AND ANTIPYRETICS.

In the normal animal heat production and heat loss are maintained at a constant level—the normal body temperature. The normal temperature of different animals is as follows:[1]

Birds.

Goose	41.70° C.
Sparrow	39.08° C. / 42.10° C.
Pigeon	41.80° C. / 42.50° C.
Turkey	42.70° C.
Guinea fowl	43.90° C.
Duck	43.90° C. / 42.50° C.
Crow	41.17° C.
Swallow	44.03° C.
Gull	37.80° C.

Mammals.

Tiger	37.20° C.
Horse	36.80° C. / 37.50° C.
Rat	38.50° C.
Hare	37.80° C.
Cat	38.30° C. / 38.90° C.
Guinea-pig	38.80° C.
Dog	37.40° C. / 39.00° C. / 39.60° C.
Panther	38.90° C.
Mouse	41.10° C.
Sheep	37.30° C. / 40.50° C.
Ape	35.50° C.
Guinea-pig	35.76° C. / 38.00° C.
Rabbit	37.50° C. / 38.00° C.
Ox	37.50° C.
Ass	36.95° C.

Anything that increases heat loss or lessens heat production will lower the temperature. This is regulated by the central nervous system. Heat output is lessened reflexly by constriction of the cutaneous vessels and heat loss increased in the same way by vasodilationa nd by sweating.

The heat-regulating center is "set" so that shivering (to increase heat production) or sweating (to increase heat loss) occurs with a slight change in the temperature.

A normal dog, with a temperature of 38.6° C., will shiver when the temperature is lowered 0.7° C., and perspire, *i. e.*, show the signs of perspiration, when the temperature is raised 0.5° C. Our knowledge of the location and mechanism of the heat-regulating

[1] Landois and Stirling, 1891, p. 406.

center or centers is still very incomplete. However, toxins, cocain and other pyrogenous poisons will derange the regulating center, and, depending on the infection or drug, the regulating mechanism instead of being set at 38.6° C. may be set at 40° C. or higher.

The sensitivity of the center to heat and cold at this higher temperature is the same as at the lower.

The reaction to cold probably means an augmented state of excitability or stimulation of the heat-regulating centers, while increase in temperature depresses them. Overheating of the carotid blood is known to depress the medullary centers, while at the same time the coöperative or reciprocal centers, sweat-glands and the respiration center (heat dyspnea) may be stimulated.

Fever is thought to be due to a stimulation of the heat-regulating centers by toxins and pyrogenous poisons. Heat puncture also stimulates these centers in the same way. The mechanism of antipyresis is not well understood, but the coal-tar antipyretics reduce the temperature in hyperpyrexia by a sedation or depressing action on the heat-regulating mechanism by "setting" the temperature mechanism at a lower state as one sets a thermostat in the laboratory.

In fever the nitrogen eliminated as urea and oxygen consumed is lessened by antipyretics, but this is a result rather than the cause of the fall of temperature, because:

1. No such result occurs in the normal individual.
2. The excessive excretion of urea does not run parallel with the increase of temperature but is generally most marked after the crisis.
3. In fever produced by the injection of bacterial toxins, increase in oxygen consumption and urea excretion occurs even when the rise of temperature is prevented.

ANTIPYRETICS.

The immediate active agent in the coal-tar antipyretics is para-amidophenol, and if this formed too rapidly, collapse may follow. Hence only those that yield para-amidophenol slowly can be used.

These coal-tar antipyretics act on the heat-regulating center to depress it, but the actual reduction of temperature is due to heat loss from the surface of the body. If the fevered animal be wrapped in a cotton blanket or placed in an incubator, so that no loss from the surface can take place, antipyrin has little effect.

Antipyrin differs from a cold bath in lowering the temperature by the fact that it has a central action and tends to permanently lower the temperature. That it acts on the heat centers in the brain

is shown by the fact that high section of the cord prevents its action and it has no local or general action as has quinin, while after a cold bath the tendency is for the temperature again to rise, due to increased heat formation. A cold bath does not at least immediately "set" the regulating mechanism. Alcohol and the nitrites dilate the superficial vessels, but do not set the center. Quinin lessens temperature by decreasing oxidation in the muscles and gland cells. The temperature fall is secondary to diminished metabolism. Quinin inhibits oxidation by oxidases *in vitro,* and it reduces the temperature of the normal animal. The action is not on the brain, since it reduces the temperature of an animal whose cord is cut. The coaltar antipyretics will not act if the cord is cut.

Experiment I.—(*a*) Take the rectal temperature of eight rabbits.

(*b*) Give each a hypodermic injection of 2 c.c. of 5 per cent. cocain per kilo.

(*c*) Record the temperature each fifteen minutes until a maximum is obtained; then give—

1. Two c.c. of 2 per cent. solution of a quinin salt; repeat every fifteen minutes until the temperature falls.
2. Wrap in cotton and treat the same as in 1.
3. Give an injection of 5 c.c. per kilo of 2 per cent. acetanilid in alcohol.
4. Treat the same as in 3. First wrap in cotton; repeat every fifteen minutes until the temperature falls.
5. Immerse in a water-bath at 25° C.
6. Immerse in a water-bath at 40° C.
7. Give by mouth 10 c.c. per kilo of 2 per cent. acetanilid solution in alcohol.
8. Give 10 c.c. per kilo of 2 per cent. antipyrin by mouth.

Make complete records and discuss the mode of action of each of these drugs.

As a control, if sufficient animals are available, treat eight other rabbits in the same way without giving the cocain.

Experiment II.—Take the temperature of eight rabbits and inject hypodermically with 1 c.c. per kilo of body weight of 20 per cent. peptone in water twelve hours before class work. Then treat as in Experiment I.

Experiment III.—Take the normal temperature and note the changes produced in the following experiments:

Hydrated Chloral.—Administer 0.3 gram of hydrated chloral to a cat (0.6 gram to a rabbit) by the rectum. Note the degree of anesthesia induced.

Morphin.—Administer 100 mg. of morphin sulphate (3 c.c. of 3 per cent. solution) per kilo to a rabbit subcutaneously (half of the relative amount to a dog); compare the anesthetic action with that of hydrated chloral. The temperature of a dog may or may not fall; that of a rabbit falls.

Antipyrin in Health.—Administer 100 mg. of antipyrin to a normal rabbit through a stomach-tube; little change in temperature. Note that the temperature of rabbits undergoes marked changes, with changes in external temperature, with careless handling, fright or excitement; hence the success of these experiments demands careful work.

Experiment IV.—Each student should record his own temperature and take 0.5 gram of antipyrin or other antipyretic. Record the temperature every hour for four hours.

Experiment V.—Record the temperature and respiration of four rabbits. Place in an adequately ventilated box and raise the temperature in the box to 43° C. by means of an electric light within the box. In two hours record the temperature again. Give two 10 c.c. per kilo of 2 per cent. antipyrin by mouth and replace in the heated box; allow the other two to remain at the room temperature without antipyrin. At the end of an hour again record the temperature and respiration. Discuss the hygienic and drug treatment of fever.

Experiment VI.—*Heat Centers.—Demonstration.*—Puncture of the median part of the corpus striatum and other parts of the nervous system often causes a rise in temperature. The centers are not definitely localized. It has been suggested that the rise in temperature in fevers is due to bacterial toxins acting on these centers and that antipyretics restore these centers to their normal state either by preventing the formation of these toxins, neutralizing them or causing their more rapid elimination. Study the mechanism of each antipyretic in the text.

Experiment VII.—1. Record rectal temperature of two rabbits: Into one inject intravenously 1 to 1.5 c.c. per kilo fluidextract of ergot and record the temperature every thirty minutes.

2. Into two, inject in same way 5 to 8 c.c. of 1 to 20 solution of calcium lactate and record temperature in the same way.[1]

Experiment VIII.—Record the blood-pressure and respiration of a dog. Lay bare the carotid and place it on a copper jacket so constructed that a stream of hot water may be circulated around the

[1] See Hill: Jour. of Pharm. and Exp. Therap.

carotid artery as it passes to the brain. What is the effect on the heart and respiration?

Experiment IX.—Anesthetize a cat or rabbit with ether. Prepare for aseptic operation. Make central incision in the skin of head along the sagittal suture. Peel back the skin and make a trephine hole 5 mm. lateral to the sagittal suture and the same distance anterior to the coronal suture. When the bone is removed, puncture with a hat-pin or small probe, directed downward until it touches the base of the skull, and is twisted around in this location. Watch the condition of the ear vessels. Close the operative wound aseptically, remove the ether and record the rectal temperature every fifteen minutes for three hours or more.[1]

[1] See Prince and Hahn: Am. Jour. Physiol., 1918, xlvi, 412. This gives references to other literature, also Gottlieb, Arch. Expt. Path. u. Pharm., 1890, xxvi, 419.

CHAPTER XVI.

PHARMACOLOGY OF THE GLANDS.

THE word glands comes from the Latin glans—acorn, referring to the shape of glands in general, (see Fig. 19, page 99.)

The function of glands is secretion. This may be external or internal.

The chief glands of external secretion are:

1. The Lacrimal.
2. Salivary.
3. Gastro-intestinal.
4. Pancreatic.
5. Liver, bile.
6. Kidneys.
7. Mammary.
8. Sweat and sebaceous.

Glands of internal secretion (endocrinal):

1. Thyroid.
2. Thymus.
3. Adrenals.
4. Liver.
5. Spleen.
6. Testes and ovaries.
7. Perhaps all glands and tissues to some extent.

Lacrimal Glands.—Function to moisten the eye.

The nerves of the lacrimal glands are: Sympathetic from the superior cervical ganglion. Parasympathetic from the fifth nerve through the lacrimal nerve.

Drugs Affecting the Gland.—The atropin group—paralyzing; the pilocarpin-eserin group—stimulation; epinephrin—stimulating.

According to the rule, atropin paralyzes the parasympathetic nerve-endings.

Eserin and pilocarpin stimulate the parasympathetic nerve-endings.

Epinephrin stimulates the sympathetic. The gland may also be stimulated reflexly over the parasympathetics through the second and seventh nerves.

Salivary Glands.—*Nerves.*—Sympathetics through the superior cervical ganglion and parasympathetics—through the chorda tympani, a branch of the seventh cranial.

Function of the Glands.—To provide fluid to moisten the buccal cavity, the food, and to secrete a digestive enzyme, ptyalin.

The nerves also supply fibers to the vessels of the gland; the sympathetic are constrictors and the parasympathetic are dilators.

Methods of Acting on Glands.—1. Directly. 2. Reflexly: Taste, smell, movements, chewing, acids and pungent tasting substances.

Direct Stimulation.—1. *Through the Chorda.*—Pilocarpin, eserin, muscarin, cholin.

2. *Through the Sympathetic.*—Epinephrin, cocain.

Depression.—3. *Through the Chorda.*—The atropin group.

Depression.—4. *Through the Sympathetic.*—Morphin—central action.

Stimulation through action on all ganglion cells—nicotin, lobelin.

Elimination of Drugs by the Salivary Glands.—Drugs are excreted in small amounts by the salivary glands.

The following have been found: Iodides, bromides, hexamethylenamin, mercurial and lead compounds, quinin and some other alkaloids, sulphocyanides.

Gastric Secretion.—*Function of the gastric glands*—secretion of digestive and diluting fluids.

Nerves.—The stomach receives both motor and inhibitory fibers from the vagus. The finer anatomy of these is not known. It is probable that there are sympathetic fibers mixed with the parasympathetic. The parasympathetic are motor; the sympathetic, inhibitory.

The secretion of gastric juice is influenced by drugs, similarly to salivary secretion, but to a lesser degree.

The pilocarpin group stimulates secretion. The atropin group diminishes it.

From a practical standpoint the action of these drugs on the stomach in diseased condition is of little value, because they act on nerve-endings, and in most diseases where stimulation is needed the gland cell is involved or destroyed. In cases of hypersecretion the atropin group of drugs are of value.

Intestinal Secretion.—The secretion of intestinal juice is somewhat influenced by mechanical, chemical and thermal stimulation, but the extent of this and the mechanism has been but little investigated.

The amount of succus entericus secreted by the small intestine has been estimated by Pregl at 3000 c.c. per day. The juice was

collected from a Thiry-Vella fistula and the total amount estimated. Succus entericus contains the following enzymes:

1. Enterokinase, which activates trypsin.
2. Erepsin.
3. Inverting or hydrolytic enzymes.
4. Nuclease, also secretin and prosecretin.

The nervous control of the secretion has not been sufficiently investigated and there is practically no known pharmacology of intestinal secretion. Most investigations of the intestine have been confined to movement, absorption and excretion.

When absorbed or given hypodermically the following drugs are excreted into the intestine, probably by the intestinal juice:

1. Ca, phosphates, sulphates, heavy metals, such as Fe, Cu, Zn, Bi, Hg. Mn, etc., morphin and other alkaloids, resinous cathartics, toxins, etc.

Pancreatic Secretion.—Function of the pancreas—the secretion of digestive juices, probably also an internal secretion.

Nerves.—Vagus and sympathetic splanchnic. The gland may be stimulated—chemically as by hormones, and through the nerves.

1. *Stimulation by Parasympathetics.*—The pilocarpin group of drugs, stimulate these nerves.

2. *Inhibition through the Parasympathetics.*—The atropin group, in small doses; large doses, in some way not understood, cause increased flow of juice.

3. Stimulated reflexly by mustard, spices, etc., acting on the duodenum.

4. Stimulated chemically through the blood by secretin, a substance found in the duodenum and which may be prepared by grinding the duodenal mucous membrane with dilute hydrochloric acid.

The two secretions—the chemical and the nervous, are different.

The chemical secretion (due to secretin) is clear, watery, rich in alkali and poor in protein or organic matter, and contains but little ferment. It occurs after the administration of atropin. The nervous secretion is thick, opalescent, rich in ferments and poor in alkali. The normal relation of the two secretions is not well understood.

Regarding the internal secretion of the pancreas, there is no pharmacology. No drugs are known which influence it.

CHAPTER XVII.

PHARMACOLOGY OF THE KIDNEYS.

THE pharmacology of the kidney is so important that the student is referred to the monograph on the "Secretion of the Urine," by Cushny,[1] for established facts, and Fischer's "Edema and Nephritis"[2] for suggestions.

1. **Nerves.**—So far as we know there are no secretory nerves to the kidney. This leaves the pharmacology a matter of circulation and direct action on the secreting cell. In all cases the act of secretion tends to dilate the vessels, and unless a drug which stimulates the secretory epithelium also constricts the vessels, it will act as a diuretic.

2. **Blood-pressure.**—Unless there is a blood-pressure of 40 mm. of Hg or more, practically no urine is secreted. After an essential pressure is established, the volume of urine secreted depends on the volume of blood going through the kidneys.

Theories of Diuresis.—Drugs can act only to modify the normal function of the kidney. This function is the secretion and excretion of urine. The mechanism of secretion is not satisfactorily understood. The student is advised to review the theories of secretion.

1. The Ludwig—filtration or physical theory.
2. Bowman—Heidenhain or secretory theory.
3. The modern view of theory which is more or less a combination of the first two, with modifications.

Important Factors Modifying the Secretion of Urine.—1. The blood-pressure: To secrete at all the general blood-pressure must be 40 mm. of mercury or over.

2. Free water must exist in the blood. Most of the water in the blood is in a colloidal or combined form. Some is being continuously absorbed and some excreted. The volume probably depends on the metabolic rate. Acids or acidosis increase the capacity of the proteins to hold water and lessens diuresis. Alkalies, salts, etc., lessen the water-holding capacity of the tissues and so increase diuresis. Many experimental facts support this theory.

3. Absorption from the tubules seems an important factor in governing the amount of urine excreted. It may be assumed that

[1] Longmans, Green & Co., 1917.
[2] Wiley & Sons.

on passage through the tubules some of the secretion water may be reabsorbed, just as it would be on passage through the intestine: Diuretic salts then, may act by preventing reabsorption from the tubules just as cathartics act by preventing absorption from the intestines. In both cases there may also be a direct stimulating action on the parenchymatous tissues.

4. *Vasodilation.*—Almost all substances on passage through the kidneys cause a vasodilation. If such substances do not injure the parenchymatous tissues they act as diuretics. Some substances which have a decided diuretic effect in minute amounts, are very harmful in slightly greater concentrations. Cantharidin and mercury are examples.

Nerves of the Kidney.—The kidney is innervated by the vagus and by the splanchnics, through the celiac ganglion. These nerves, however, are not secretory but govern the vessels. The splanchnic is the chief motor nerve of the kidney and each is distributed to the kidney of the same side.

Diuretics.—Since there are no secretory nerves to the kidney, diuretics must act, either: 1. By increasing the volume of blood through the kidney.

2. By direct stimulation of the secreting cells.
3. By lessened absorption from the tubules.
4. By liberation of colloidal water from the tissue cells.
5. By a combination of all or any of these possibilities.

Give the evidence for and against each of these possible mechanisms.

The chief diuretics are:

1. Caffein compounds.
2. The digitalis groups—in some conditions—edema.
3. Pituitary extract—not used for this purpose.
4. Salines—especially alkaline and absorbable salts.
5. Alkaline iodides.
6. Mercurials—especially when there is little catharsis.

Antidiuretics.—All substances that increase sweating without the introduction of fluid:

1. Pilocarpin.
2. Arecolin.
3. Antipyretics.
4. Heat.
5. Camphor.
6. Large doses of opium.
7. Ammonium acetate and citrate.

CAFFEINE

An alkaloid existing in coffee, tea, guarana, and cola nut.

Classified as:

Cerebral stimulant.
Cardiac stimulant.
Respiratory stimulant.
Diuretic.

Physiologic action:

Nervous System.

Cerebrum. Stimulates cortex, increasing the activity of psychic functions.

Medulla. Stimulates respiratory center and vasomotor center. Vagus center may be stimulated, but the effect masked by the direct effect upon the heart.

Muscular System. Irritability and working power of muscle tissue increased.

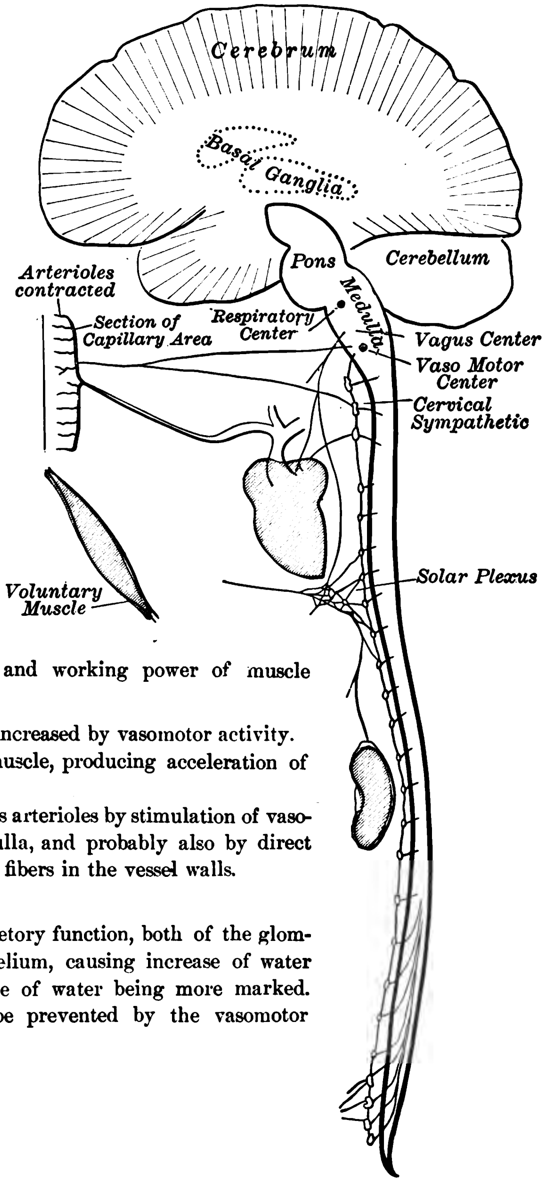
Circulation. Arterial pressure increased by vasomotor activity.

Heart. Stimulates heart muscle, producing acceleration of the pulse.

Capillary area. Contracts arterioles by stimulation of vasomotor center in the medulla, and probably also by direct action upon the constrictor fibers in the vessel walls.

Excretion.

Kidneys. Stimulates excretory function, both of the glomeruli and the renal epithelium, causing increase of water and of solids, the increase of water being more marked. The diuretic effect may be prevented by the vasomotor action.



The red color indicates stimulation by Caffeine.

Elimination of Drugs by the Kidneys.—Practically all drugs that are absorbed may be eliminated more or less by the kidney. They may, however, be partially oxidized or conjugated before elimination. Some drugs that injure the kidney to any great extent may prevent the flow of urine and therefore may be but slightly eliminated by that channel.

Make a record of the excretion of each drug studied.

Theories of Urinary Secretion as Outlined by Cushny in Secretion of Urine.—At present there are three theories of urinary secretion:

1. The Bowman—Heidenhain theory.
2. The Ludwig theory.
3. The modern theory, which is more or less of a combination of the other two theories, and has been built up by studying the others. It takes part of both and rejects parts of both, and is not yet satisfactory in all details. The following is a summary of the essential points and differences of each theory.

	Bowman. Heidenhain.	Ludwig.	Modern theory.
Functions of capsule	Secretion by vital activity	Filtration purely physical	Filtration purely physical.
The filtrate is . .	Deproteinized plasma	Deproteinized plasma	Deproteinized plasma.
Volume of filtrate	Approximately same as urine	Somewhat larger than urine	Very much larger.
Tubular epithelium, functions of	Primarily secretory; some absorption under exceptional conditions	Considerable infusion to blood under exceptional conditions	Purely absorption, but a selective absorption.

The modern view accepts the filtration and absorption of Ludwig, but supplements them when necessary by the vital activity postulated by Heidenhain. According to the modern theory the secretion of urine consists of two distinct processes: (1) A purely physical process which consists of a filtration through the glomerulus. (2) Selective reaborption through the tubules; this selective absorption depends on the vital activity of the epithelium.

CAFFEIN.

Caffein is used mainly as (1) a diuretic, and (2) as a stimulant to respiration and circulation; (3) for its influence on muscle, and (4) for its action on the nervous system. Experiments will illustrate this action.

1. **The Diuretic Action of Caffein.**—Caffein compounds are the diuretic drugs *par excellence.* Many laboratory exercises on this

point fail because they do not consider the fundamentals of urine secretion or the condition in which caffein acts best as a diuretic. First, the kidneys cannot secrete water unless water is present. While the blood normally contains over 90 per cent. water, this water is apparently in combination with colloid material and only free water can be secreted. In those clinical cases where caffein compounds act to the best advantage, the tissues are water logged either because of inadequacy on the part of the heart or changes in the proteins or salt retention. Caffein under these conditions causes a diuresis either by causing a greater elimination of the free water or by liberating some of the combined water. In normal animals the change caused by caffein on diuresis is so small that, as a class experiment, it is unsatisfactory. Only as much water as is taken in can be poured out, and in normal conditions this pouring out or urination proceeds at a constant rate and is hastened but little by diuretics. To make a laboratory experiment show the real action of caffein on the kidneys, the animal should be given a large volume of liquid a short time before the caffein is administered.

Mechanism of the Action of Caffein Compounds on the Kidney.—The action of caffein is direct on the kidney because:

1. There are no secreting nerves to the kidney; it occurs after section of all nerves and on the isolated kidney, and after degeneration of the nerves.

2. The fluids in the other tissues are not changed.

3. The kidney increases in volume, when secreting. (*a*) The action therefore is local, but may be either on the vessels—a circulatory action or

(*b*) It may be an action on the secreting cell. Opinion at present favors a direct action on the secreting cell:

1. Because Rost[1] has found that the flow of urine is increased—only when considerable caffein passes into the urine.

2. Richards and Plant[2] have shown that diuresis occurs with caffein even when there is no change in kidney volume.

Experiment I.—*Action of Caffein on the Heart, Respiration and Kidneys.*—1. Prepare a dog for blood-pressure and respiratory tracing and for injection into the femoral vein. Insert urethral cannulæ and by means of a Y-tube unite these so that the excretion from both kidneys flows from a single tube. Record the secretion in drops by means of a signal magnet; also measure it.

[1] Arch. f. Anat. u. Physiol., 1901, p. 534.
[2] Jour. of Pharm., 1915, vii, 485.

2. Make a tracing showing the normal blood-pressure, respiration and urine secretion for fifteen to thirty minutes.

3. Inject into the femoral vein 5 per cent. of the weight of the animal of 0.9 per cent. NaCl.

4. Measure the urine secretion as before for fifteen to thirty minutes.

5. Inject slowly into the vein 10 mg. per kilo weight of caffein, diuretin or augurin. Note the influence on blood-pressure, respiration and urinary flow for thirty minutes. Compare results with 2, 3 and 4.

6. After the action of caffein has been studied inject 10 c.c. per kilo of warm 8 per cent. sodium sulphate every five minutes or until the secretion of the urine is increased markedly. While the flow of urine is rapid, inject 10 c.c. per kilogram of body weight 6 per cent. mucilage of acacia and note the effect. This has been recommended by Bayliss in cases of hemorrhage, since it sustains blood-pressure better than physiological saline. It does this because it holds water in the bloodvessels.

Experiment II.—Diuretics frequently while raising the pressure or stimulating the kidney constrict the kidney vessels and to this extent work against the flow of urine, since this flow depends on the volume of blood circulating through the kidney. To avoid this chloral is sometimes prescribed with the diuretic as a "corrective." It is given with digitalis for the same reason.

Prepare a dog as in Experiment I: (*a*) Take tracings of normal blood-pressure, respiration and urine flow and injection into femoral vein. Inject 1 c.c. of 1 per cent. caffein per kilo body weight. Repeat the dose every ten minutes for three times and get records of the effect for thirty minutes. Then (*b*) inject intravenously 0.3 gram per kilo of chloral hydrate (3 c.c. 10 per cent.). Take three to five minutes for this injection. Compare the rate of secretion before and after the administration of chloral. (*c*) Acetates are sometimes prescribed to aid in diuresis. The superiority of theobromin sodium acetate as a diuretic is somewhat due to the acetate. Inject 1 gram per kilo of sodium acetate (10 c.c. 10 per cent. per kilo) and note results for thirty minutes. Potassium acetate is frequently prescribed with infusion of digitalis; why not use it here? Has it any advantages over sodium acetate?

Experiment III.—*Action of Caffein on the Frog.*—Inject 2 c.c. of 0.5 per cent. caffein in water into the anterior lymph sac and make observations every few minutes. Notice the changes in irritability

—muscle cramps and a final paralysis. (Note the solubility of this alkaloid in water.)

Compare the actions of caffein, strychnin and picrotoxin.

Experiment IV.—*Action of Caffein on the Frog's Heart.*—Pith a frog and take heart tracings by the suspension method. Isolate and stimulate the vagus. Drop 1 per cent. of caffein solution slowly on the heart; take tracings and note whether or not there is any change in the vagus action. Continue the tracing until definite action is obtained.

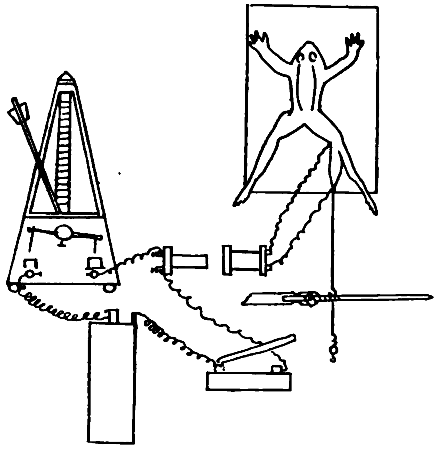


FIG. 40.—Method of arranging muscle for recording fatigue contractions.

Experiment V.—*Action of Caffein on the Turtle Heart.*—Pith a turtle, expose vagi and take a record of the heart by the suspension method. Test irritability of both vagi. Irrigate the heart with 0.5 per cent. caffein by dropping the solution directly on the heart. Determine whether or not there is any change in the irritability of the vagi.

Experiment VI.—*The Action of Caffein on Turtle Heart Strips.*—Prepare and take tracings of a ventricle strip suspended in 0.8 per cent. saline. When a good record is being obtained add sufficient 2 per cent. caffein in the same solution so that the concentration of the liquid in which the strip beats is 0.1 per cent. caffein. After thirty minutes change the concentration to 0.5 per cent. caffein; continue this until definite action is obtained.

Experiment VII.—*Action of Caffein on the Reflex Time of Frogs.*—Pith the animal and prepare for reflex time as under alcohol either by Türck's method or by electrical stimulation. Determine the average time of five reflexes. Then inject 1 c.c. of 0.5 per cent.

caffein in water into the anterior lymph sac and after fifteen minutes again determine the reflex time. Take average of at least five determinations.

Experiment VIII.—*Action of Caffein on Respiration.*—Anesthetize a small dog with ether and prepare to measure blood-pressure, and respiratory volume with a spirometer. Place a cannula in the femoral vein for injection. Take a normal tracing and measure the expired air in minute intervals. Measure volume per minute and respiratory rate. Also make record of the respiration on the drum from the chest movements. This can be done by a rubber tube around the chest to which a tambour is attached.

When normal tracings and volume measurements are obtained, inject 1 c.c. of 3 per cent. morphin slowly into the femoral vein and note the changes in respiration every five minutes for fifteen minutes. Then inject intravenously 0.5 c.c. per kilo of 1 per cent. solution of caffein and again measure as before. Repeat injections if necessary. Tabulate results.

Experiment IX.—Repeat Experiment IX under cocain, page 148, but use 1 c.c. 0.5 per cent. caffein.

SALINE DIURETICS.

All salts which are eliminated by the kidney are diuretics. In class experiments, sodium sulphate is often used and given intravenously. However, when sulphates are given by mouth they are so slightly absorbed that little diuresis results. This is especially true if they produce catharsis. One must distinguish carefully between the theoretical and practical value of such procedures. Only salts that are absorbed and are excreted by the kidneys are practical diuretics. KNO_3 is diuretic when given by mouth; if it is given intravenously, the potassium is so depressant that the action of the potassium may be so great that it will injure the heart. Potassium or sodium acetates are the most used. They have a double action, first the salt action, and second the alkaline reaction. They are oxidized to carbonates in the body.

Salts may act as diuretics in three ways:

1. By direct action on the kidney.
2. By lessening the water-holding capacity of the body colloids.
3. By increasing the alkalinity, as in the case of the acetates.

Acidosis decreases the urinary flow by increasing the water-holding capacity of the body colloids.

Experiment I.—Prepare a dog for measurement of blood-pressure, respiration and urine flow. Inject intravenously 5 per cent. of the animal's weight of 0.85 per cent. of NaCl solution.

1. Measure urine flow for thirty minutes.

2. Inject slowly 20 c.c. of $\frac{N}{10}$ acid (HCl). Watch carefully that the injection does not kill the animal. Measure the urine for thirty minutes.

3. Inject 40 c.c. $\frac{N}{10}$ of Na_2CO_3 slowly and measure the urine for thirty minutes.

4. Inject slowly 3 per cent. of KNO_3 until the heart shows symptoms of depression. Measure the urine for thirty minutes.

5. Inject 30 c.c. of 10 per cent. Na_2SO_4 and measure the urine for thirty minutes.

6. Inject 10 c.c. of $\frac{N}{10}$ HCl and note the influence on the flow of urine.

7. Inject 10 c.c. of $\frac{N}{10}$ Na_2CO_3 and note the effect for thirty minutes.

Experiment II.—*Diuretic Action of Caffein on the Normal Animal.* —1. Select a male rabbit. Catheterize until the bladder is empty.

2. At the end of an hour catheterize again and measure the amount of urine.

3. Inject subcutaneously 10 mg. per kilo of body weight of citrate caffein in water.

4. At the end of an hour catheterize again and measure the volume of urine.

5. Compare and discuss the results. What do you conclude as to the diuretic action of caffein.

Experiment III.—1. A group of from ten to twenty students should work together. Each one should empty the bladder completely at the beginning of the experiment.

2. Then each one should drink 300 c.c. of water.

3. At the end of an hour empty the bladder and measure the volume of the urine.

4. Then each person should drink 300 c.c. of water, one-third of the students taking 2.5 grains of caffein, one-third 5 grains and one-third 10 grains.

5. At the end of one hour empty the bladder and measure the volume of urine.

6. Compare results and discuss briefly the diuretic action of the caffein.

7. A second group should carry through this same experiment but without drinking any water.

PHENOLSULPHONEPHTHALEIN.

Kidney Function.—This drug is not used in therapeutics, but as a diagnostic test of kidney function. When the kidneys are normal, about 60 to 80 per cent. of this is excreted within two hours after the hypodermic injection.

Experiment I.—Take seven rabbits and place each in a separate clean metabolism cage. Two days before the experiment inject—

1. With 2 c.c. per kilo of 1 per cent. arsenious acid, As_2O_3, subcutaneously.
2. With 1 c.c. per kilo of 10 per cent. potassium bichromate.
3. Each day for three days preceding the experiment, 1 c.c. per kilo of 0.5 per cent. uranium nitrate.
4. Mercuric chloride, 5 c.c. per kilo of 0.2 per cent. for two days preceding the experiment.
5. Five c.c. per kilo of 5 per cent. ammonium oxalate.

6 and 7. Controls.

Empty the bladder of each and inject hypodermically 2 c.c. of a 6 mg. per cubic centimeter solution of phenolsulphonephthalein. Also give each one 20 c.c. of 0.9 per cent. NaCl. In two hours empty the bladder of each one and determine how much of the phenolsulphonephthalein has been excreted. Compare with the controls. What is the condition of the animals at this time?

Experiment II.—Anesthetize each of the animals with ether. Insert a bladder cannula for collection of urine and a cannula in the jugular vein for injection of solutions. Wait ten minutes between each injection and measure the urine for each period.

1. Inject 20 c.c. of 0.19 per cent. NaCl.
2. Inject 5 c.c. of 2 per cent. sodium citrate.
3. Inject 2 c.c. of 0.05 per cent. citrated caffein.
4. Inject 10 c.c. of 0.5 per cent. theobromine sodium salicylate.
5. Inject 2 c.c. of 0.5 per cent. calomel in 1 per cent. sodium thiosulphate.

Make a chart showing the effect of each drug on each animal and compare with the normal animals.

Experiment III.—Inject subcutaneously with aseptic precautions 2 c.c. of a 0.5 mg. solution containing per cubic centimeter of phenolsulphonephthalein into 10 students. In one or two hours determine the amount excreted.

If a colorimeter is not available the amount of coloring material can be determined as follows: (*a*) Place the urine in a 500 c.c. or

1000 c.c. graduate; add sufficient NaOH to color. Make up to 100 c.c. or 200 c.c. mark.

(*b*) Place 0.5 mg. per cubic centimeter of phenolsulphonephthalein or the amount injected subcutaneously in another graduate of the same size. Alkalinize with NaOH and dilute until the color matches the urine. From the degree of dilution of the standard required to match the urine the percentage excreted can be determined.

CHAPTER XVIII.

PHARMACOLOGY OF SWEAT-GLANDS.

Function.—The sweat-glands are excretory organs for salts and water mainly. There is some nitrogenous matter also, but not of sufficient amount to reckon in metabolic experiments. In cases of uremic poisoning and other pathologic states the nitrogen elimination by the sweat-glands may be increased.

Distribution of the Glands.—1. In man and horses the whole surface of the skin contains sweat-glands.

2. In dogs and cats sweat-glands are found on the feet only.

3. Rabbits, rats and mice have no sweat-glands.

Innervation.—The sweat-glands are under the direct control of sympathetic nerves and the drugs acting on the secretion of sweat act mainly on the nerve-endings, although there are centrally acting diaphoretics.

We do not know that any drugs act directly on the glands. The striking peculiarity of the nerves to the sweat-glands is that although sympathetic they are stimulated by pilocarpin and paralyzed by atropin in a manner similar to autonomic nerves; likewise epinephrin is without influence on them. They provide the one great exception to the rule that epinephrin stimulates sympathetic nerve-endings and pilocarpin stimulates autonomic endings.

Drugs that act on the nerves governing the secretion of sweat may act (1) centrally and (2) peripherally.

The drugs acting on the sweat centers are ammonium salts, picrotoxin, camphor and strychnin to some extent.

The proof that they act centrally is that they fail to act after section of the nerve to the part or after high section of the cord. The location of the sweat center is not definitely known. It is, however, above the fifth spinal segment, because cases in the human are known in which fractures at this level, with injury to the cord, stopped sweating below the injury, not above. The center is probably located in the medulla. In the cat, in addition, it has been established that there are at least two spinal sweat centers, one for the forelimbs in the lower cervical and another for the hindlimbs in the dorsal region. Diaphoretics acting on the nerve endings are pilocarpin, muscarin, eserin, and arecolin.

Proof that the action is peripheral, is that they act after section of the nerves. Other drugs and agents acting centrally. Most drugs that exert an antipyretic effect act centrally and in large doses cause sweating.

The sudorific glands are affected in the same way as the sweat-glands, but have not been so carefully studied.

ENDOCRINAL PHARMACOLOGY.

Concerning the pharmacology of the endocrinal glands, we must say that more numerous experiments have been made in feeding glands and extracts and some definite results on blood-pressure, respiration, etc., have been gotten, but regarding the modification of the function of each of these glands by drugs or otherwise, little has been learned. Those glands like the adrenals that have a nervous mechanism, can be stimulated by drugs like nicotin and perhaps depressed by general depressants, but little of anything definite has yet been learned.

CHAPTER XIX.

PHARMACOLOGY OF THE LIVER, MAMMARY GLANDS, UTERUS AND BLADDER.

PHARMACOLOGY OF THE LIVER.

Main Functions of the Liver.

1. Secretion of bile.
2. Carbohydrate transformations.
3. Sympathetic functions.
4. Interrelative functions with other organs.

Secretion of Bile.—This is controlled by the vagus and splanchnic nerves.

Drugs Influencing the Formation of Bile are Termed Cholagogues.—The bile stimulants are:

1. Bile itself.
2. Bile salts.
3. Soaps.
4. Albuminoses.
5. Dilute HCl.
6. Salicylates and benzoates.
7. Calomel.

Drugs Stimulating movement of the Gall-bladder.—Pilocarpin.

Drugs Lessening Movement of Gall-bladder.—Atropin. Atropin is frequently used in gall-stone colic because of this property.

Excretion of Drugs by the Bile.—Cu, Pb, Hg, menthol, methylene blue, amyl alcohol, hexamethylenamin and other drugs have been reported in the bile. They occur, however, only in traces, except hexamethylenamin, which is said to be excreted in quantities sufficient to sterilize the bile.

The Glycogenic Function of the Liver.—This is influenced by a large number of drugs, but the action may be indirect. In fact, while it is well known that the liver is exceedingly important in carbohydrate metabolism, the mechanism of the action is little understood, and while the action of many drugs on this metabolism has been studied to some extent, it is the harmful action that has been most studied. Very little is known of drugs that have a beneficial

effect on the glycogenic function of the liver. The harmful effect is usually manifested by an increase in the sugar content of the blood and by glycosuria, though a hypoglycemia may also occur.

Drugs Influencing the Carbohydrate Metabolism of the Liver.—

1. Epinephrin is necessary for the normal process; in large amounts hypodermically it causes glycosuria.

2. Salts injected intravenously cause hyperglycemia and glycosuria.

3. It may be influenced in the same way by many drugs acting on the nervous system, as strychnin, caffein and others.

4. Certain other drugs which greatly depress the animal, like hydrazins, peptons, etc., given intravenously, may cause hypoglycemia.

The other chemical functions of the liver, like the formation of urea, its action in fat metabolism, its function in blood coagulation, etc., are markedly influenced by the internal secretions of other glands like the thyroid, adrenals, etc., and also by chemical agents. The actions of phosphorus, hydrazin, arsenic, etc., on the liver are striking.

PHARMACOLOGY OF THE MAMMARY GLANDS.

The function of these is milk secretion. They are markedly influenced by the internal secretion of the ovaries, and probably they give *off an internal secretion*, but distinct evidence of this has not been presented. Drugs theoretically might stimulate or decrease the volume of milk secreted. As a matter of fact, however, drugs have little influence on milk secretion.

Nerves.—Experimental investigation shows that the mammary gland is little, if at all, under the direct influence of the nervous system. That such nerves exist, however, is unquestionable, as shown by the marked influence of emotional states on milk secretion.

Mackenzie,[1] from an investigation of the mechanism of milk secretion, concludes that:

1. The secretory activity of the gland is not under the influence of the nervous system.

2. Agents that modify the secretion reach the gland by the blood.

3. Extracts of the pituitary, corpus luteum, pineal body, the uterus and the mammary gland itself stimulate secretion.

4. The pituitary gland is the most active stimulant.

5. Inhibitory hormones are produced by the fetus and placenta.

[1] Quart. Jour. of Exp. Physiol., 1911, iv, 305.

6. Drugs such as pilocarpin and atropin that influence the secretion of most glands are without effect.

7. Because of the ineffectiveness of the drugs mentioned in (6). it is concluded there are no demonstrable secretory nerves to these glands. This is supported by electrical stimulation of nerves going to the glands.

Lactagogues.—Practically there are none. The secretion of milk is said to be lessened by the administration of KI and by the local application of belladonna. In the latter case the analgesic action on the sensory nerves, may be confused with an action on the secretory mechanism.

Elimination of Drugs in the Milk.—Iodides, bromides, salicylates antipyrin, arsenic, mercury, hexamethylenamin, morphin, atropin, etc., have been found in the milk of animals.

PHARMACOLOGY OF THE UTERUS.

The uterus, like the intestine, is in more or less continuous movement. These movements are automatic, that is not initiated by nerve impulses, but controlled by the nerves.

The motor nerves are autonomic, from the nervus pelvicus (Erigen's) and inhibitory from the sympathetic from the hypogastric plexus.

Drugs modifying uterine movements, may act:

1. On the muscle directly. (*a*) Hypophysis extracts, (*b*) barium salts and (*c*) ergot.

Hypophysis acts directly on the muscle and causes maximal contraction. Barium also acts directly on the muscle and stimulates it.

2. On the ganglion cells. (*a*) Nicotin: The result of nicotin varies, depending on the species of animal and the predominating ganglion cells, much in the same way as epinephrin.

3. On the nerve-endings.

Epinephrin.—The uterus receives sympathetic nerves from the hypogastric plexus. The action of epinephrin is identical with stimulation of this plexus, but it differs in different animals. The uterus receives through the sympathetic both motor and inhibitory fibers. The predominating action varies with the animal and with the condition of the animal. Thus, stimulation of the hypogastric nerves of the non-pregnant cat causes inhibition. In the pregnant state it causes contraction. In the rabbit the usual result in all cases is contraction. In the dog, contraction is followed by inhibition. Epinephrin acts similarly to stimulation of this plexus.

Atropin.—In small doses atropin may increase the action, but in larger amounts always inhibition. This is the usual atropin action on autonomic nerves, except the primary stimulation which in most regions is absent.

Physostigmin and Pilocarpin.—These drugs exert their usual action on antonomic nerve ends—stimulation.

Ergot.—The fluidextract of ergot is the principal preparation used in medicine. The recent work of Dale has simplified greatly the knowledge of ergot action. It contains three active ingredients: ergotoxin, tyramin and ergamin.

Ergotoxin and tyramin act like epinephrin and stimulate the myoneural junction of the true sympathetic nerves. There are some differences, however, between the action of epinephrin and these. The action and differences are as follows:

1. Epinephrin acts on both motor and inhibitory nerves, and under special conditions, therefore, may cause a fall of blood-pressure.

2. Ergotoxin stimulates the vasoconstrictors only. Large doses may paralyze these, so that after ergotoxin, epinephrin may cause a fall in blood-pressure.

3. Tyramin acts on both motor and inhibitory nerves, but only to a small extent on the inhibitory.

4. Ergamin does not act on the nerve-endings at all, but on the non-striated muscle directly.

5. Different samples of ergot may differ in action, depending on the relative amounts of these bases present. Also in pregnant animals when there is a development of sympathetic nerves the action varies from that in the non-pregnant animal. Study these actions in detail from the text.

Experiment I.—Action on the frog; take three frogs; give one 0.5 c.c. of fluidextract ergotæ. Give the second 1 c.c. and the third 2 c.c. Inject into the abdominal lymph sac.

Experiment II.—*Action of Ergot on the Arterioles.*—(*a*) Place a frog on the boards and examine the capillary circulation of the web of the foot. Make a sketch of the field and give the animal 0.5 c.c. fluidextract ergotæ and repeat observations at five-minute intervals.

(*b*) Repeat (*a*), using 1 c.c. of the fluidextract.

(*c*) Repeat (1) and (2), using the mesentery instead of the foot for observations.

Experiment III.—*Action of Ergot on the Blood-pressure, Respiration, Pupil and Vagus Tone.* Prepare a dog for blood-pressure and respiratory tracings. Insert a cannula in the femoral vein for injec-

tion. Isolate a loop of the intestine for observation of the action on the capillaries. Make normal tracings and inject the fluidextract of ergot, 0.5 c.c. at a time, and repeat every five minutes until the animal dies. Note the action on the heart, respiration, pupil and intestines. A tracing of the intestinal movements may be taken by one of the methods under epinephrin.

Experiment IV.—*Action of Ergot on the Heart Strips.*—Prepare a heart strip, and when it is beating regularly add fluidextract of ergot gradually until the bath contains 10 per cent. of the fluidextract.

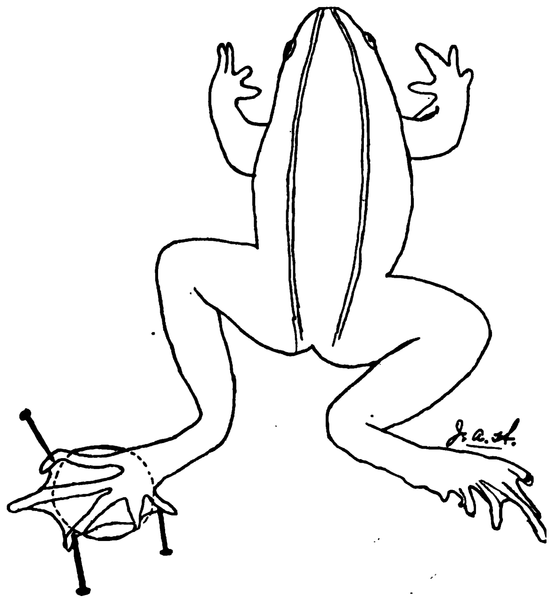


FIG. 41.—Frog on cork plate to show method of preparation for studying the circulation in the web of the foot.

Experiment V.—*Action of Ergot on the Uterus.*—Take segments of the uterus of a guinea-pig, cat or rabbit and arrange for tracing as with a heart strip. Keep the bath at 40° C. When it is contracting rhythmically, add, drop by drop, some fluidextract of ergot.

In the preparation of uterine strips certain precautions are necessary to get results.

1. An anesthetic if used in removing the uterus acts to prevent the rhythmical movements.

2. Shock or brutal manipulations have the same effect. It is best to remove the head of the animal quickly with a pair of large scissors or a sharp knife. Then the uterus is removed quickly, using

a forceps and scissors—do not handle—and place in well-aërated warm (40° C.) saline, and always handle with these precautions in mind.

Experiment VI.—Study the effect of ergot on the uterus when injected intravenously by Barbour's method.

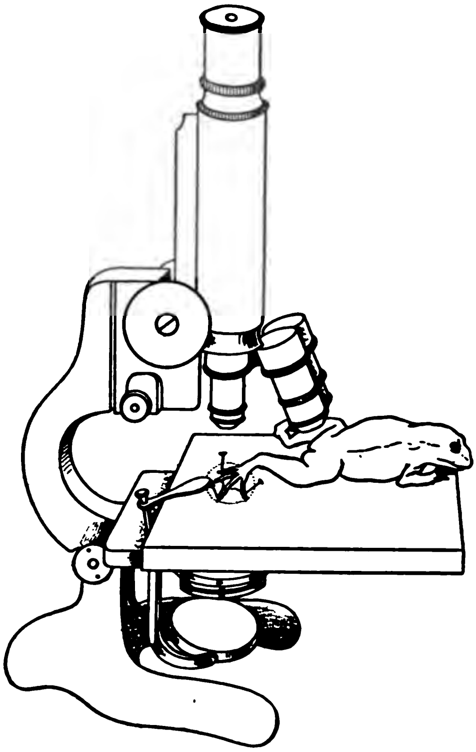


FIG. 42.—Method of examination of circulation in the web of a frog's foot. The apparatus consists of a cork plate with a hole in it.

Experiment VII.—*Standardization of Ergot.*—No satisfactory method is available. Three more or less satisfactory methods are used:

1. Blood-pressure method.
2. Cock's-comb method.
3. The uterine method: (*a*) Isolated Uterus: Experiment V; (*b*) *in situ:* Experiment VI.

The blood-pressure method is the easiest and perhaps the most reliable. 0.08 c.c. of the fluidextract per kilo of body weight should cause a rise in blood-pressure of 30 mm. Hg. in the dog.

Anesthetize a dog with ether. Keep the anesthetic regular and prepare for blood-pressure and respiratory tracings. Prepare for injection into the femoral vein. Then proceed as follows:

1. Take normal tracing of about three inches on the drum. Then stop drum.
2. Inject 0.04 c.c. per kilo body weight of the fluidextract and wait five minutes.
3. Take a three-inch tracing on the drum. Stop drum and wait five minutes.
4. Then take another tracing. Keep this up until three or four tracings are taken. The blood-pressure of each will be different.

If the first injection causes a fall in pressure of more than 35 mm. Hg. or a rise of more than 50 mm. Hg., the dose should be reduced one-half. If the fall is less than 25 mm. or the rise less than 24 mm. the dose should be doubled.

5. The same animal may be used for three or four injections if one allows sixty minutes to elapse between injections.

Experiment VIII.—*The Cock's-comb Method.*—This method is used by some manufacturers to determine the strength of an unknown quantity of ergot by comparing its effects with the effects of an equal quantity of standardized ergot. Leghorn cocks with large combs and wattles are advised; they are used in preference to the others because the common barnyard fowl varies too greatly in its reaction. The cock to be used must not be fed for twenty-four hours previously.

Examine the color, temperature and general appearance of the comb and wattles. Then with a hypodermic syringe inject deep into the breast muscles 5 c.c. of a first-class preparation of fluidextract of ergot. The drug may also be given into the crop with a soft-rubber catheter.

Place the animal in a quiet place and observe it carefully, from time to time, for at least one or two hours. Do you note any change in the appearance of the comb and wattles? If so, at what time after the injection is the change at its maximum? If you had a standardized preparation and a non-standardized preparation of the fluidextract of ergot, could you compare the relative strengths of these two solutions by their relative actions in the same sized doses on roosters of approximately the same size, age and sensitivity to the drug? Note the action on the intestine. The method is not very satisfactory.

PHARMACOLOGY OF THE BLADDER.

The bladder is merely a reservoir. The muscular coat is strengthened at the cervix by a circular coat, which acts as the sphincter vesicæ internus, while around the urethra on the outside of the bladder is the sphincter vesicæ externus. When the urine accumulates to a certain extent the pressure reflexly stimulates the sphincters.

Nerves.—The bladder receives motor fibers from the second to the third sacral nerves—autonomic—through the N. Erigentes from the hypogastric plexus. It also receives sympathetic fibers from the second to the fifth lumbar nerves, reaching the bladder through the inferior mesenteric ganglion. Local application of epinephrin will usually cause a relaxation. Atropin is given in cases of enuresis to inhibit the urinary reflex by an action on the autonomic nerve-ends. The small amounts that escape in the urine in therapeutic doses could scarcely exert this influence.

Antisepsis.—Various drugs are given in cystitis, etc., with the idea of disinfecting the urine. Among these are (1) hexamethylenamin, which acts only in acid reaction; (2) sodium benzoate and salicylate, (3) various volatile oils such as copaiba, cubeb, oleum santali. A study of these comes more directly under antiseptics, than under the dynamics of the bladder.

CHAPTER XX.

PHARMACOLOGY OF THE MUSCLES.

THE muscles are divided into two great groups:

1. Voluntary:
   Mastication.
   Respiration.
   Locomotion.
2. Involuntary:
   Cardiac.
   Smooth.

The function of muscles is contraction. This results in motion, oxidation, reduction, etc., with consequent formation of heat and chemical changes.

Stimulation may result in:

1. Greater contraction.
2. More prolonged contraction.
3. The ability to do more work.
4. Greater chemical activity.

Drugs may cause stimulation or depression (1) by acting directly on the muscle; (2) indirectly through the nerve; (3) indirectly through the circulation.

VOLUNTARY MUSCLES.

Why one group, the voluntary, should be under the control of the will and another, the involuntary, should be beyond the control of the will cannot be answered. The fact that in one case, voluntary, the motor nerves arise in the brain anterior to the fissure of Rolando and that the effector neurone goes direct from the anterior portion of the cord to the muscle, does not explain the control of this group. As far as we know, one set should be as much under the control as the other. Again, why one set may be paralyzed by curara and another by atropin, or why one set should be stimulated by epinephrin and another by acetyl cholin or pilocarpin, is beyond our grasp at the present time. It is probably due to chemical differences which at present we do not know.

INVOLUNTARY MUSCLES.

Gaskell[1] subdivides the involuntary muscles according to their innervation (based on their development) into the following groups:

1. The vascular group, which includes all vessels, and is supplied with motor fibers from the sympathetic alone—constrictor and dilator.

2. The dermal or ectodermal group, which includes those muscles immediately underneath the skin, pilomotor, muscles of sweat-glands, etc. The motor cells all belong to the sympathetic.

3. The endodermal group, which lies under the surface of the gut and is innervated by both enteral parasympathetic and sympathetic.

4. The urogenital-dermal system or group, which is derived from the segmental duct. This includes all the muscles surrounding the Wollffian and Müllerian ducts, and since these ducts arise from the segmental duct it may be called the segmental duct system of involuntary muscles.[2] It includes the muscles of the Fallopian tubes, uterus, ureters, vas deferens, bladder, rectum and large intestine or all muscles innervated by the lumbar splanchnic nerve through the inferior mesenteric ganglion. Both motor and inhibitory nerves in this system, according to Gaskell, belong to the sympathetic system. The innervation is not reciprocal, *i. e.*, not from two systems of nerves, as in the gut.

5. The sphincter muscles of the gut, bladder and urethra, which receive motor fibers from the sympathetic. These sphincter muscles contract under the influence of epinephrin—act like the pilomotors —and Gaskell considers they have a similar origin.

6. The group of muscles connected with the adjustment of vision, which has a reciprocal innervation.

According to the reaction to drugs, these muscles, therefore, may be placed in two classes: Groups 1, 2, 4 and 5 are all united by the sympathetic nervous system and contract with small doses of adrenalin. Group (3) contracts with acetyl cholin and is known as the acetyl-cholin group. Gaskell considers that both motor and inhibitory nerve cells of the segmental duct system belong entirely to the sympathetic system and are not in any way connected with the enteral system. He does not use the modern classification, but essentially the same thing. He classifies the involuntary system into: (1) Sympathetic or bulbo, and (2) enteral or sacral.

[1] The Involuntary Nervous System, 1916.
[2] Gaskell: The Involuntary Nervous System, p. 40.

More recent work has shown that the sacral autonomic system sends motor fibers to the uterus, rectum, bladder, anus and external genitals, and in this region there still remains much uncertainty regarding the innervation and the action of drugs. The pharmacology of the muscles, *i. e.*, the direct action of drugs on the muscle is less important than the pharmacology of the nervous mechanism regulating muscular activity.

Gaskell's classical work shows the necessity for further investigation in the pharmacology of this region.

General proofs that a drug acts directly on a muscle are: 1. When the action is direct on the muscle it is the same on all muscles and not as in the case of adrenalin which acts on nerve-endings, and causes contraction in one location and relaxation in another.

2. The action occurs after the nerves have degenerated.

3. The action occurs in muscles where motor nerves do not exist, as in the bloodvessels of the lungs, brain, etc.

While the direct action on the muscle exists in many cases, the most important action on muscles is, as a rule, through the nerves and the blood. Drugs may stimulate or depress muscle, as they influence function.

Drugs which act directly on muscle:

Caffein.
Digitalis.
Veratrin.
Alcohol.
Pituitrin.
Barium and heavy metals.
Physostigmin.
Aconitin.
Saponin.
Emetin.
Cocain, quinin, etc.

Classification of Drugs Acting on Muscles.

I.—*Drugs which diminish the power of striated muscle:*

Quinin.
Chloral.
Chloroform.
Potassium salts.
Ammonium salts.
Lithium salts.

II.—*Drugs which increase the power of striated muscle to do work:*
- Alcohol.
- Veratrin.
- Barium.
- Calcium.
- Digitalis bodies.
- Glycerin.
- Sugar.
- Caffein compounds.

III.—*Drugs which increase the irritability of striated muscle.*
- Physostigmin.
- Aconitin.

IV.—*Drugs which depress smooth muscle:*
- Nitrites.
- Organic nitrates.

V.—*Drugs which stimulate smooth muscle:*
- Barium, pituitrin.

VI.—*Drugs which stimulate cardiac muscle:*
- Barium.
- Caffein bodies.
- Digitalis bodies.
- Calcium salts.

VII.—*Drugs which depress the cardiac muscle directly:*
- Potassium salts and narcotics of the aliphatic series, especially chlorin compounds.
- Bile salts.

PITUITARY EXTRACT, LIQUOR HYPOPHYSIS, PITUITRIN, INFUNDIBULIN, ETC.

In studying this drug it should be compared with epinephrin, digitalis, ergot, barium and the nitrites.

Experiment I.—Inject 0.5 c.c. of liquor hypophysis into the anterior lymph sac of a frog and note the action.

Experiment II.—Arrange a frog on the board for the study of the circulation through the web of the foot or the mesentery. Make a sketch of the condition of the vessels. Inject 0.5 c.c. liquor hypophysis into the anterior lymph sac and watch closely for some minutes for any change that may occur in the circulation. After ten minutes observe at fifteen-minute intervals for two hours.

Experiment III.—*Action of Liquor Hypophysis on the Heart.*—(*a*) Take a tracing of the contractions of the heart of a frog or turtle

by the suspension method. Test the action of vagus stimulation. Irrigate with a 1 to 5 solution of liquor hypophysis. After some time again test the efficiency of vagus stimulation.

(*b*) Irrigate with a 0.1 per cent. atropin sulphate until the vagus action is eliminated and again try the action of liquor hypophysis.

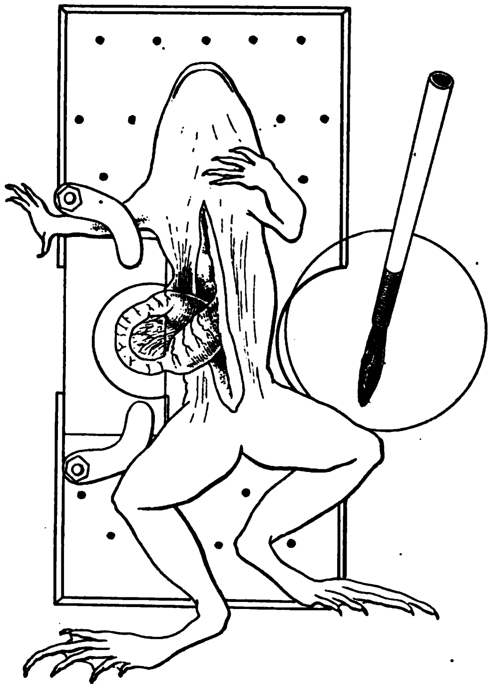


FIG. 43.—Preparation for examining the circulation in the frog's mesentery. The preparation can be placed under a microscope.

Experiment IV.—Repeat Experiment III, using atropin before liquor hypophysis. (Section *b*, III.)

Experiment V.—Prepare turtle heart strips, and when these are beating rhythmically, add liquor hypophysis, drop by drop, and note the action.

Experiment VI.—*Action of Liquor Hypophysis on the Heart, Respiration, Pupils and Kidneys.*—Anesthetize a dog and prepare for blood-pressure and respiration tracings. Insert catheters in the uterus or bladder for measuring the flow of urine. Note the condition of the pupil. Insert a cannula in the femoral vein for injection. Isolate and test the vagus response to stimulation.

1. Take normal tracing.

2. Inject 2 c.c. of a 1 to 5 solution of liquor hypophysis into the femoral vein. Repeat if necessary until definite results are obtained. Make a record of the change.

3. When the action is marked, stimulate the vagus.

4. Inject 1 c.c. of 1 to 10,000 epinephrin and compare its action at all points with liquor hypophysis.

5. Repeat 2. When satisfied with the comparison, isolate a loop of the intestine and make a record of the intestinal movements in the usual way.

6. Inject 2 c.c. of 1 to 5 solution of liquor hypophysis.

7. When definite action is obtained in 6, inject 1 c.c. of 1 to 10,000 epinephrin.

8. Inject slowly 5 c.c. of 0.5 per cent barium chloride.

The Main Action of Liquor Hypophysis.—1. An action on smooth muscle structures such as the heart, vessels, bladder, uterus, intestines, seems to bear no relation to innervation, since the pulmonary and coronary vessels constrict decidedly.

2. It increases oxidation and metabolism and stimulates the growth of skeletal and connective tissues.

3. Excessive doses cause nervous symptoms.

4. It alters the susceptibility to many poisons (Hunt's nitril reaction) increases some (morphin) diminishes others (nitrils).

5. It acts as a hormone in the development and action of other glands, the kidneys and sexual especially. In studying this drug, watch for evidences for or against these statements.

Preparation of Uterine Segments for the Study of the Action of Infundibular Extracts.—The uterus of a guinea-pig or cat is the most suitable, but the uterus of any animal will answer. Virgin or non-pregnant uteri give the best results. To remove the uterus from the body the animal is bled to death without an anesthetic. Anesthesia inhibits or prevents the uterine movements to a considerable extent. Shock also prevents uterine movements and must be avoided. It is best to decapitate the animal quickly with a sharp instrument. Then quickly remove the uterus and handle it with special care. Do not take it up in the fingers but handle with warm forceps and cut with sharp scissors. Place it immediately in a vessel of warm aërated saline. Remove segments for testing contractions by cutting under the saline bath. Use segments about 2 cm. in length. Success with uterine strips demands that they be carefully handled at the correct temperature and that they be adequately aërated.

Experiment VII.—*Action of Liquor Hypophysis on the Uterus.*—(a) Prepare a uterine segment for recording contractions. When it is

contracting rhythmically add 0.01 c.c. of liquor hypophysis and note the result. If this does not cause an increase in the contraction, increase the amount added until it does. The actual result will vary with different uteri and the result can be judged only by comparing the effect of the solution added, with the effect of a standardized preparation. (See Method of Standardizing.)

(*b*) Study the action of liquor hypophysis on the uterus *in situ* by Barbour's method; inject the drug into the femoral vein.

Experiment VIII.—*Standardization of Pituitary Extracts.*—The action on the blood-pressure as well as the action on the uterus has been advocated as a means of standardizing pituitary extracts. The blood-pressure method is as follows:

0.05 c.c. of standard pituitary should give an average rise in the blood-pressure of 30 mm. Hg. when injected into the femoral vein of a dog 8 to 12 kilos in weight. The extracts found on the market vary from 10 to 20 per cent. extracts of the gland. But some 10 per cent. extracts are as strong as other 20 per cent., hence the need of standardization. If the preparation tested shows a blood-pressure rise of less than 24 mm. Hg. the dose should be increased, while if the rise is more than 40 mm. Hg. the amount injected should be lessened. The objections to the blood-pressure method of standardizing pituitary extracts are:

1. In clinical work pituitary extract is used almost entirely for its action on the uterus. The action on the blood-pressure may bear no relation to the action on the uterus, since pituitary extract contains two principles, a pressor and a depressor. The pressor principle is easily destroyed. Both principles act on the uterus.

2. Repeated observations cannot be made on the same animal, since liquor hypophysis is less easily oxidized in the body than epinephrin and cannot, like this, be repeatedly injected with the same effect.

3. The blood-pressure is a rather stable thing and not readily influenced. Great variations in the strength of solutions of the pituitary body may obtain, and this method will fail to show it. Roth, however, found that commercial pituitary extracts vary less in blood-pressure effects than in their effects on the uterus.

4. Variations in the depth of anesthesia cause marked changes in the blood-pressure rise.

Uterine Method of Standardization of Pituitary Extract.—For every gram of the fresh posterior lobe, finely ground and minced, 5 c.c. of 0.1 per cent. acetic acid is added and sufficient water to make 1 c.c. of water for each gram of the gland. The mixture is boiled

for ten minutes, filtered and made up to 10 c.c. One c.c. of this filtrate represents 0.1 gram of the fresh gland. Dried material may be used if calculated in terms of fresh material. Twenty parts of dried material are equal to 100 parts of fresh. On autoclaving to sterilize the solution loses some of its strength, but after that it will keep indefinitely. A solution of this kind may be used as a standard. The average of solutions prepared in this way when diluted 20,000 times should have the same activity on the isolated uterus of the virgin guinea-pig as a 1 to 2,000,0000 solution of beta-amino-azolyl-ethylamin hydrochloride, when tested as directed by the U. S. Hygienic Laboratory Bulletins Nos. 100 and 109. This method is essentially that given in Experiment VII above.

NITRITES.

The main action of the nitrites on the heart and circulation are:

1. The vessels are dilated through loss of tone, due to direct action on the muscle of the vessel. The action is on the vessel wall, since it bears no relation to innervation, and the coronaries and pulmonaries dilate.

2. The rate of the heart is accelerated, due to the low pressure lessening the effect of the vagus.

3. The formation of methemoglobin.

VERATRIN.

Veratrin is but little used in therapeutics. It has several definite actions which should be studied and compared with other drugs, especially barium chloride and aconitin.

The main actions of veratrin are:

1. An aconitin-like action on the sensory nerves.

2. A peculiar characteristic stimulation of the muscle substance, which leads to a persistence of muscle tone, with prolonged relaxation.

This action is a stimulation because:

1. Fatigue, or fatigue products like KCl, or lactic acid prevents it.

2. The muscle under veratrin will do more work.

Experiment I.—Make a 2 per cent. oleatum veratrinæ by triturating 2 grams of veratrin in 5 c.c. of olive oil in a mortar. Warm the mortar and add 50 c.c. of oleic acid. Continue stirring until the veratrin is dissolved, then add 45 c.c. of olive oil. Take 2 c.c. of this and rub thoroughly over the course of a nerve. What are the symptoms? This is sometimes used in neuralgias.

Experiment II.—Inject 0.5 c.c. of 0.01 per cent. veratrin into the abdominal lymph sac of a frog. Compare this with a normal animal. Watch for one hour.

Experiment III.—Count pulse and respiration in each animal and give a cat, dog and rabbit 0.5 c.c. per kilo body weight of 0.1 per cent. veratrin hypodermically. Note the symptoms and changes from normal.

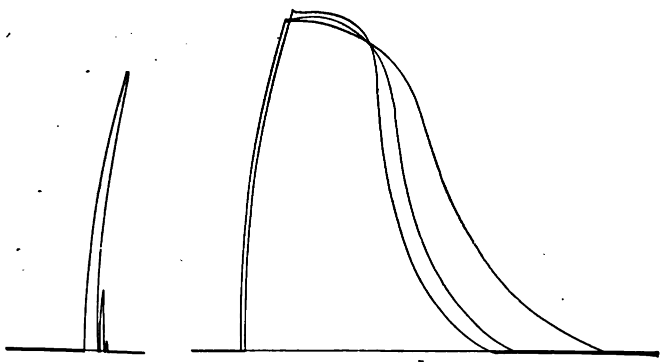


FIG. 44.—Tracings of muscular contractions from the gastrocnemius of the frog *a*, normal; *b*, three successive contractions taken at intervals of one minute, five minutes after the injection of veratrine. The contraction is higher and much more prolonged than in *a*, and the lever returns very slowly to the base line. (Cushny.)

Experiment IV.—Ligate one leg of a frog so as to shut off the circulation. Inject 0.5 c.c. of 0.1 per cent. veratrin into the abdominal lymph sac. After thirty minutes prepare the muscle of each leg for a single contraction record. What is the difference in the normal and veratrinized muscle? Tracings.

Experiment V.—Prepare a dog for blood-pressure and respiration tracings. Place a cannula in the femoral vein for injection; take a normal tracing and inject 1 c.c. of 0.1 per cent. veratrin every five minutes until the animal dies.

Experiment VI.—Veratrin on the turtle heart strips. Take normal tracings, measure the volume of the fluid in which the strip is contracting and take tracings when this contains 0.0001, 0.0003 and 0.0006 per cent. veratrin.

QUININ.

Quinin is a general protoplasmic poison, with a specific action on the malarial plasmodium. It has also an antipyretic action.

Experiment I.—(*a*) *Action on Yeast Fermentation.*—Make up a 10 per cent. solution of glucose in 1 per cent. NaCl and place in a fermentation tube. Inoculate with yeast.

(*b*) Make a 10 per cent. solution of glucose in 1 per cent. quinin bisulphate. Inoculate with yeast and place both samples in an incubator at 40° C. and compare the rate of fermentation.

Experiment II.—Inject 1 c.c. of 0.1 per cent. quinin bisulphate into the anterior lymph sac of frog and place in a quiet place. Count the rate of the lymph heart and note changes in the general reactions of the animal.

Experiment III.—*Action of Quinin on White Corpuscles.*—Pith a frog; pin to a cork plate and expose the intestine with mesentery intact for observation of the circulation with a microscope. Isolate a field in which one can see the circulation. Look especially at the white cells and note their relation to the vessel wall. When a normal tracing has been obtained, inject 1 c.c. of 0.5 per cent. quinin bisulphate into the anterior lymph sac and watch carefully for changes in the behavior of the white cells.

Experiment IV.—*Action of Quinin on the Frog or Turtle Heart.*—Take a tracing by the suspension method. Irrigate the heart slowly with 0.05 per cent. quinin bisulphate. After thirty minutes use 0.1 per cent.

Experiment V.—*Quinin on the Heart and Respiration of a Mammal.*—Count the respiration and heart-rate of a dog. Inject 5 c.c. of 0.2 per cent. quinin bisulphate into the femoral vein without an anesthetic and record changes. Repeat with larger doses if thought advisable.

Experiment VI.—Anesthetize a dog. (*a*) Prepare for blood-pressure and respiration tracings. Isolate and cut the right vagus and prepare for stimulation of the central and peripheral ends. Place a cannula in the femoral vein.

(*b*) Take normal tracings and stimulate each end of the vagus separately.

(*c*) Inject 2 c.c. of 0.1 per cent. quinin bisulphate into the femoral. Study changes of the action on the vagus.

(*d*) Repeat (*c*) with increasing doses until definite action is obtained.

Experiment VII.—*Quinin Urea Hydrcchloride.*—Inject an area of a dog's leg with 1 per cent. quinin urea hydrochloride. Compare the efficiency of this with 0.01 per cent. cocain hydrochloride. In three minutes after the injections, determine whether or not the areas are sensitive to pain.

Experiment VIII.—Take 5 grains of quinin bisulphate in water. After one hour collect the urine and apply the Thalleoquin test as follows:

(*a*) To about 10 c.c. of the urine add 3 c.c. fresh bromine or chlorin water. Then add gradually an excess of ammonium hydroxide, or

(*b*) Add a drop or two of ammonia to the urine and extract with ether. Evaporate the ether, add a drop of 5 per cent. HCl and dissolve the residue in water. Test as in (*a*).

Experiment IX.—Heat a piece of cinchona bark in a dry test-tube. If quinin is present a carmine colored vapor will be given off.

CALCIUM, BARIUM AND MAGNESIUM SALTS.

Experiment I.—*Action on the Frog's Heart.*—Excise the hearts of six frogs and place in watch-glasses. Note how long they continue to beat in the following solutions.

1. Ringer's solution.
2. Ringer's without Ca.
3. Ringer's without K.
4. NaCl 0.8 per cent.
5. Distilled water.
6. 0.7 NaCl in 0.1 per cent. sodium oxalate. Explain results.

Experiment II.—Prepare a dog for blood-pressure and respiratory tracing.

(*a*) Slowly inject sodium oxalate until the heart begins to fail. Now inject 0.1 per cent. $CaCl_2$.

(*b*) Inject 1.0 c.c. of 1 per cent. KCl and repeat if necessary until the heart is markedly depressed. Then repeat the injection of $CaCl_2$.

(*c*) Isolate a loop of intestine for observation or for tracing of movement. Inject slowly into the femoral vein 5 c.c. of 0.2 per cent. $BaCl_2$; watch the blood-pressure and condition of the intestine. When the intestine contracts markedly, inject about 10 c.c. $CaCl_2$ slowly and observe results. Place a few drops of warm $CaCl_2$ directly on the gut.

Experiment III.—*Calcium and Magnesium Antagonism.*—Give a rabbit a subcutaneous injection of 5 c.c. of 25 per cent. $MgSO_4$ per kilo. In about thirty minutes anesthesia follows. Now rub a little toluol on the veins of the ear to dilate them. Clamp the vein with a bulldog clamp and inject into the vein slowly about 8 to 10 c.c. of 3 per cent. calcium. What is the effect? Rabbits are very easily killed by air embolism.

Experiment IV.—Prepare several turtle heart strips. Place 1 (*a*) in normal saline. When it is beating rhythmically add a sufficient quantity of barium chloride to make the solution 0.01 per cent.

(*b*) To number (2) in the same way add sufficient $CaCl_2$ to make it 0.03 per cent. When there is marked action on the beat exchange (*a*) and (*b*). If an exchange cannot be made conveniently change the solution in both.

CHAPTER XXI.

PHARMACOLOGY OF THE LYMPHATICS.

Lymph is the colorless fluid which fills the lymphatic vessels and surrounds the tissue elements. The movement is from the tissue to the veins and this movement is due to (1) the difference in pressure of the lymph at its origin and the pressure in the larger veins, (2) to the movement of the muscles, etc., (3) to the movements of respiration, and (4) in certain animals, notably the frog, it is due to the rhythmic action of lymph hearts.

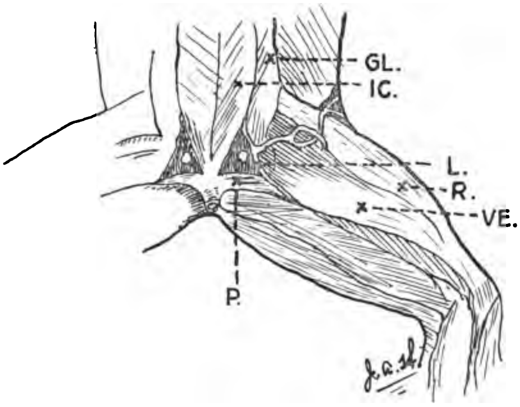


Fig. 45.—Posterior lymph hearts in the frog. The beating of these hearts will facilitate the spread of a drug in the frog after the blood heart has been removed, *L*, posterior lymph hearts; *GL*, gluteus muscles; *IC*, iliococcygeus; *P*, pyriformis; *R*. rectus; *VE*, vastus externus. (After Ecker.)

The physiology of lymph formation is not settled, therefore the pharmacology must be somewhat incomplete. Certain facts are definite, but depending on whether we consider the lymph a secretion or a filtration the explanation will vary. Ludwig taught that lymph is formed by filtration, and in minor degree by diffusion.

Heidenhain believed that lymph is secreted by the capillary epithelium.

Drugs that cause a flow of lymph are called lymphagogues. Heidenhain classifies these:

Class I: Peptone.
Leech extract.
Extract of crayfish muscle.
Egg albumen.

Protein substances, these increase the amount, specific gravity and the total solids of the lymph—probably due to injury of the vessels—inflammation.

Class II: Salts, sugar, etc. Crystalline substances that increase the volume but cause a more watery lymph.

Experiment I.—Anesthetize a dog and record arterial pressure, insert a cannula into the thoracic duct and measure the flow of lymph. Now inject slowly 5 c.c. of a 5 per cent. peptone solution and note the changes in lymph flow and blood-pressure. Repeat until definite action is obtained.

Experiment II.—Repeat Experiment I, using potassium iodide sugar, etc. Test the lymph for presence of the drugs used.

Experiment III.—Test the effect of pilocarpin and atropin on the flow of lymph as in the previous experiment.

An extract from the lymph glands of animals has been employed in exophthalmic goiter, lymphadenoma and other glandular swellings, but the results are not thought to be of any permanent value.

From a practical standpoint the flow of lymph must be influenced through the factors that are most concerned in its circulation, viz.:

1. The circulation of the blood.
2. The condition of the muscles.
3. Respiration.

The fact that the atropin or pilocarpin have no influence on the flow of lymph, indicates that it is not a secretion.

CHAPTER XXII.

GENERAL PROTOPLASM POISONS AND MISCELLANEOUS.

HYDROCYANIC ACID.

Hydrocyanic acid is a general protoplasmic poison. It is classified by Loew a "substituting" poison because it reacts with the aldehyde group forming substitution products. The nature of the combination is so strong that it is fatal. It is for this reason a general protoplasmic poison. The main actions of the cyanides are:

1. A destructive action on enzymes.
2. Primary stimulation and paralysis of the nerve and medullary centers.
3. A paralysis of the oxidative processes in the muscle.
4. An action on the blood-formation of methemoglobin and cyanhemoglobin? (See Fig. 55, page 239.)

Experiment I.—Drop 1 c.c. of 5 per cent. KCN solution into the mouth of a small cat. Note carefully the symptoms.

Experiment II.—Count the heart-beat and respiration of a dog and inject intravenously 1 c.c. of 1 per cent. NaCN or KCN. Record results.

Experiment III.—*Action of the Cyanides on Respiration, Blood-pressure, and Blood and Oxygen Consumption.*—(*a*) Give a dog a hypodermic injection of 2 c.c. of 3 per cent. morphin sulphate.

(*b*) In thirty minutes anesthetize with ether and prepare for blood-pressure and respiration tracings and measure the exhaled air with a spirometer. Place a cannula in the femoral vein for injections.

(*c*) Take normal tracings and measurements.

(*d*) Inject 1 c.c. of 0.1 per cent. sodium cyanide per kilo. If there is a noticeable effect, measure the change in the expired air.

(*e*) Repeat with double the dose of the cyanide.

(*f*) When asphyxial symptoms become marked, examine the blood microscopically and with the spectroscope.

(*g*) Take 0.5 c.c. of blood and test its action on hydrogen peroxide as in the beginning of the experiment.

(*h*) Hydrocyanic acid is supposed to combine with loosely-bound sulphur in proteins to form HSCN, which is not nearly so toxic

as HCN. For this reason sulphides have been advised as antidotes in cyanide poisoning.

(*i*) When the symptoms of asphyxiation are marked, run into the femoral vein 1 c.c. of 5 per cent. sodium sulphide or calcium sulphide. Run this in slowly as sulphides are also toxic. Repeat the sulphide injection if necessary.

(*j*) If the animal shows a return toward normal, make complete records.

(*k*) Repeat the sulphide injection if it is thought advisable.

Collect urine at the end of each experiment with the cyanides and test for sugar.

ACIDS, ALKALIES AND CORROSIVES.

Experiment I.—Prepare an animal for blood-pressure and respiration tracings. Insert a cannula in the femoral vein for injection from a burette.

(*a*) Take normal tracing.

(*b*) Inject slowly until symptoms of marked depression are apparent, $\frac{N}{10}$ HCl or any other acid.

(*c*) When respiration or heart shows signs of collapse, quickly inject the same amount of $\frac{N}{10}$ Na_2CO_3.

(*d*) Repeat (*b*) and (*c*). If animal is still living, use for one of the following experiments.

Experiment II.—*Corrosive Action of Acids and Alkalies.*—These experiments should be carried out on animals that have been used for some other work, as it is not necessary to waste animals for these experiments alone.

Respiration and blood-pressure tracings should be taken at the same time. The animals should be deeply anesthetized.

Inject 50 c.c. of the following solutions through a stomach tube, and after thirty to sixty minutes remove the stomach with the esophagus and the upper part of the small intestine. Spread on a white paper or plate for comparison.

(*a*) 50 c.c. NaOH, 40 per cent.
(*b*) 50 c.c. NH_4OH, concentrated.
(*c*) 50 c.c. HNO_3, concentrated.
(*d*) 50 c.c. HCl, concentrated.
(*e*) 50 c.c. H_2SO_4, concentrated.
(*f*) 50 c.c. phenol, 95 per cent.
(*g*) 50 c.c. phenol plus 95 to 100 c.c. glycerin.
(*h*) 50 c.c. cresol.

(*i*) 50 c.c. picric acid concentrated in water.
(*j*) 50 c.c. acetic glacial.
(*k*) 50 c.c. phosphoric, 50 per cent.
(*l*) 50 c.c. $HgCl_2$, 0.1 per cent.

Experiment III.—Set up four fermentation tubes with 10 per cent. glucose. Inoculate with yeast. Keep:

1. For control.
2. Make slightly acid with HCl.
3. Make weakly alkaline with Na_2CO_3.
4. Make strongly alkaline with NaOH.

Compare the rate of fermentation at 40° C.

Experiment IV.—Put about 10 grams of muscle or glandular tissue in each of seven test-tubes and cover with:

1. Concentrated H_2SO_4.
2. Concentrated HCl.
3. Concentrated NaOH.
4. Concentrated acetic acid.
5. Phenol 95 per cent.
6. Concentrated HNO_4.
7. Tincture iodin.

After fifteen minutes wash off the chemical and compare with the original.

SULPHIDES.

The sulphides are readily absorbed and excreted by the lungs.

Experiment I.—Compare this with ammonia. Anesthetize a dog. Insert a tracheal cannula. Take blood-pressure tracing from the carotid and respiratory tracing from the abdomen. Inject slowly 1 per cent. sodium sulphide or ammonium sulphide into the femoral vein and hold a piece of paper moistened with silver nitrate or lead acetate at the tracheal cannula. Note the time necessary to detect the excretion of the sulphide.

Experiment II.—Repeat with calcium sulphide. Determine the toxic dose and the cause of death. This has been advised in mercuric chloride poisoning.

Experiment III.—*Action of Sulphides on Yeast Fermentation.*—In a series of fermentation tubes containing 10 per cent. cane sugar containing yeast add:

1. 0.01 per cent. sodium or potassium sulphide.
2. 0.05 per cent. sodium or potassium sulphide.
3. 0.1 per cent. sodium or potassium sulphide.
4. Control.

What is the effect on fermentation at 40° C.?

Experiment IV.—Coat the hairy surface of the arm with a layer of CaS, prepared by running H_2S into milk of lime, and in a few minutes scrape it off with a scalpel. What is the result?

Experiment V.—Examine the chest of an anesthetized animal with a stethoscope. Allow to inhale the fumes of dilute H_2S. Continue the inhalation until symptoms of edema take place. State findings and give explanation.

OXALATES AND FLUORIDES.

Experiment I.—(*a*) Put a pinch of powdered sodium or potassium oxalate into a test-tube. Add 5 c.c. of blood and shake. Compare the clotting time of oxalated blood with normal blood.

(*b*) Use potassium or sodium fluoride as in (*a*).

Experiment II.—(*a*) Anesthetize a dog and prepare for blood-pressure and respiratory tracings. Inject slowly into the femoral vein 0.1 per cent. sodium oxalate. When depression is marked inject 1 per cent. calcium chloride slowly. Oxalates are general protoplasmic poisons, because they precipitate calcium salts and calcium is necessary to the life of protoplasm.

(*b*) Use 0.1 per cent. potassium fluoride as in (*a*).

IODIDES..

1. **Excretion.**—Take 0.5 gram KI in a capsule. After fifteen minutes collect about 5 c.c. saliva, add a few drops of H_2SO_4 and an equal volume of 1 per cent. sodium nitrite and shake with 5 c.c. of chloroform. If I is present it will dissolve the chloroform with a violet color. Repeat every five minutes until I is detected. Then again in twenty-four hours. Test the urine in the same way.

2. Twelve students in groups of six each should study the absorption of iodides from the gastro-intestinal tract as follows: Six study the time of absorption and excretion on an empty stomach, *i. e.*, 11 A.M. or 4 P.M., and the other six immediately after a midday meal. Compare the average time of absorption as manifested by the above tests. The results with the iodides will, in general, hold good for the other drugs. What is the philosophy of giving drugs sometimes before, sometimes after meals?

3. Many of the uses and supposed benefits of the iodides can be studied only in clinical cases. Their mode of action is still obscure.

HEAVY METALS.

These have a local and a general action. The local action is due to their combining with the proteins. The general action appears only after absorption and is manifest mainly on the kidney, circulation, and central nervous system.

1. Test the action of a few drops of 5 per cent. $AgNO_3$, $HgCl_2$, Fe_2Cl_6, $CuSO_4$, $Pb(C_2H_3O_2)_2$ and $ZnSO_4$ on a solution of egg white or blood serum.

2. Give a dog 5 mg. per kilo of mercuric chloride. Watch this animal for several days or until he dies. Note especially heart-rate, nervous symptoms and the action on the kidneys as manifested by the urine and by the postmortem.

3. Action on yeast: Shake a cake of yeast in 500 c.c. of 2 per cent. dextrose. Fill a series of fermentation tubes. Keep one for control and to the others add 0.1 c.c. and 1 c.c. of the solution in Experiment I. Note the results in thirty minutes and in twenty-four hours.

Local Action.—Heavy metals unite with proteins to form proteinates.

The proteins may play the part either of acid or base.

These salts are not true chemical compounds, *i. e.*, they are not of definite composition. The amount of the heavy metal in the precipitate varies. The precipitating action on proteins causes the heavy metals to act as astringents, and it also explains the vomiting caused by the heavy metals. As astringents they may act in three ways:

1. By the formation of albuminates, with the liberation of free acids, and the acid also causing some astringent action.

2. The metal may be absorbed locally and so constrict the local vessels.

3. The insoluble salts, like bismuth subnitrate, may cover and protect the surface mechanically.

General Action.—The general action of the heavy metals is seen only after prolonged ingestion.

The general symptoms and actions of the heavy metals differ mainly in the rate of absorption. There is little difference in the toxicity of arsenic and iron when injected into the blood.

Mercury is the only heavy metal which is absorbed from the alimentary canal in sufficient quantity to produce acute poisoning other than corrosive.

Chronic poisoning arises because excretion is slower than absorption.

Symptoms of Metallic Poisoning.—Gastro-intestinal.—Loss of appetite, pain and discomfort, nausea, vomiting, purging, hemorrhages and congestion. Ulcers may occur if the animal lives long enough. Lead and some others may induce constipation and griping, but they may also elicit purging.

Kidney.—Irritation, inflammation, cirrhosis, etc.

Circulation.—Little direct action; late in poisoning some action may result from disorders of nutrition.

Some dilation of the vessels of the intestines and fall of blood-pressure. In the case of lead the vessels may be constricted and pressure high. The blood, as a rule, less alkaline, is due to the increase of lactic acid.

Central Nervous System.—As a general rule, stimulation of some parts and depression of others. Delirium, hallucinations, mania, stupor, coma. Convulsions indicating that the motor areas, basal ganglia and spinal cord are affected. The different types of convulsions may occur. Lesions of the brain have been found. Peripheral neuritis, especially with lead and antimony. This neuritis does not differ from that caused by alcohol or toxins.

Metabolism.—Some of them may in small amounts produce changes similar to that produced by phosphorus.

Colloidal Heavy Metals.—Copper, platinum, silver, etc., are sometimes used in medicine. The basis for their use is the action of minute amounts of copper on infusoria and other unicellular organisms.

POTASSIUM SALTS.

Experiment I.—*Absorption and Excretion.*—(*a*) Take 0.5 gram KI in a capsule and test the saliva every ten minutes for the presence of the salt, as follows: Place the saliva in a test-tube or on a white tile and acidify with a drop of nitric acid, then add a few drops of 1 per cent. starch paste. A blue color indicates the presence of iodin.

(*b*) Collect the urine every fifteen minutes; add a few drops of nitric acid and a few drops of the starch paste.

Experiment II.—*Action of Potassium Salts on the Heart and Vessels.*—Prepare a turtle heart strip, and when it beats rhythmically in saline, add KCl so that the fluid contains 0.01 per cent KCl, 0.02, 0.04, 0.08 and 1 per cent. When depression is marked, replace the solution with 0.9 per cent. NaCl solution.

Experiment III.—*Action of Potassium on Reflex Time.*—Pith a frog and study the reflex time by Türck's method. Inject 0.5 c.c. of

potassium bromide and determine the change in reflex time after thirty minutes.

Experiment IV.—Anesthetize a dog and take blood-pressure and respiration tracings; inject 1 per cent. of KCl slowly until the heart is markedly depressed. Then inject 10 c.c. of 1 per cent. $CaCl_2$. Repeat with KCl.

AMMONIUM.

Experiment I.—Give a dog 2 c.c. of 3 per cent. morphin sulphate hypodermically; after thirty minutes count the heart and respiration-rate. Now inject 5 c.c. of 2 per cent. ammonium chloride per kilo and note the changes in the rate of the heart and respiration. Anesthetize the animal; prepare for blood-pressure and respiration tracings and for injection into the femoral vein. Slowly inject 1 per cent. ammonium chloride until spasms develop. Notice the character of these and compare with strychnin. Finally, give sufficient strychnin to produce tetanus.

Experiment II.—*Inhalation of Ammonia.*—Give a dog 2 c.c. of 3 per cent. morphin hypodermically. In thirty minutes anesthetize with ether. Prepare for blood-pressure and respiratory tracings. Isolate the vagi, but *do not cut.* When the animal is well anesthetized let him inhale a 10 per cent. solution of NH_4OH. What is the result? Now cut the vagi and continue the inhalation. If spasms do not develop soon, let him inhale 20 per cent. ammonia. Note the strength of the solution. If allowed to inhale a weak solution the absorption is so slow that spasms do not develop readily. Note the condition of the lungs at the end of the experiment.

Experiment III.—Count the pulse and respiration of a rabbit. Hold a piece of cotton with ammonia to the nose of the animal or blow the ammonia vapor into the nostrils. Stoppage of the respiration or slowing or temporary arrest of the heart follows. Trigeminal vagus reflex.

Experiment IV.—In a series of frogs inject into the abdominal lymph sac:

1. 0.2 c.c. of 5 per cent. ammonium chloride.
2. 0.5 c.c. of 5 " " "
3. 1.0 c.c. of 5 " " "
4. 2.0 c.c. of 5 " " "

If convulsions develop, note the type. Pith or destroy the brain and the medulla. How does the action of ammonia differ from strychnin?

EXPERIMENTAL GLYCOSURIA.

This may be caused by:

1. Lesions of the nervous system.
2. Asphyxia.
3. The intravenous injection of salts and drugs.
4. By the subcutaneous, intravenous or intraperitoneal administration of epinephrin.
5. By the action of phloridzin.
6. Excessive use or administration of sugar.

The mechanism of the action in any case is not well understood.

Experiment I.—Inject 1 or 2 c.c. of 1 to 1000 epinephrin subcutaneously into a rabbit. In two hours catheterize and test the urine for sugar. Too large a dose of epinephrin administered may kill the animal.

Experiment II.—Give a rabbit $\frac{1}{4}$ gram of phloridzin dissolved in 5 c.c. of olive oil subcutaneously. In an hour catheterize and test the urine for sugar.

Experiment III.—Draw blood from the femoral or jugular vein of a dog and determine the amount of sugar by the Benedict method (page 242).

Inject into the abdominal cavity 1 gram of phloridzin dissolved in about 7 c.c. of olive oil. In one or two hours catheterize and test the urine for sugar. The amount may also be determined. Test the sugar concentration of the blood when the sugar appears in the urine. Give a rabbit a hypodermic injection of 3 c.c. of 3 per cent. morphin. Collect the urine after two hours and test for sugar. Is there any change in the type of respiration? Is Cheyne-Stokes type manifest? Morphin causes glycosuria by asphyxia.

Experiment IV.—Anesthetize a cat and inject a molecular length of the solution of sodium sulphate slowly into the femoral or jugular vein. Cats are easily killed by the injection of sulphates if it is made too rapidly. Collect the urine and test for sugar frequently.

Experiment V.—Give a dog or cat 1 gram of potassium cyanide by mouth in 50 c.c. of water. When death occurs collect the urine and test for sugar with Fehling's solution.

BERNARD'S METHOD OF PUNCTURING THE FLOOR OF THE FOURTH VENTRICLE (PIQÛRE).

The instrument he used is shown in the figure (Fig. 46). The end of the instrument is thin and chisel-like and fashioned for boring. A

very thin central point, about 1 mm. long, and needle-like, extends beyond the fluted end. This sharp point punctures the floor of the

FIG. 46.—The instrument to make the puncture (piqûre).

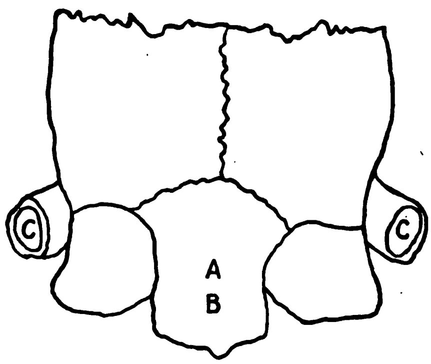


FIG. 47.—Occipital bone of the rabbit, showing landmarks for piqûre as described by Bernard. On the head of the rabbit the finger is run along the central line until one feels the tuberosity, *A*, which corresponds to the superior occipital process *B*. Immediately behind this process (*B*) the needle or drill is worked through the bone *C*, *C*, auditory tubes.

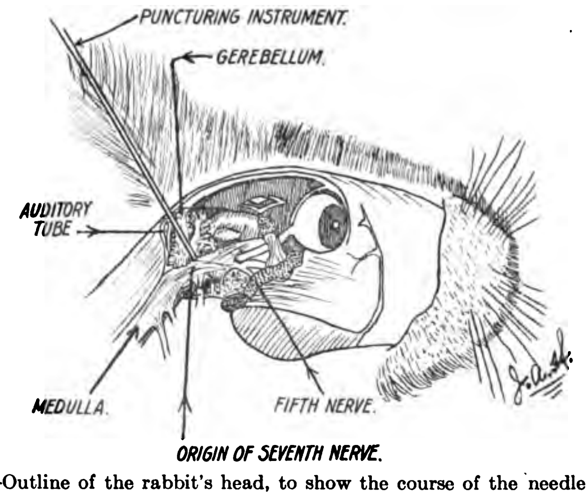


FIG. 48.—Outline of the rabbit's head, to show the course of the needle in piqûre. (After Bernard.)

fourth ventricle between acoustic and pneumogastric nerves. To accomplish this the animal's head is held in the left hand, with an assistant holding the feet. The finger of the right hand is passed over

the skull until one feels the tuberosity figure (Fig. 47). Just posterior to this tuberosity the instrument is inserted between the spongy tissue and the bone. By a boring pressing movement the instrument is forced through the bone into the cranial cavity. The instrument is then directed obliquely to the middle point between the angles of the animal's lower jaw (Fig. 48) or to cross a line which extends from one ear to the other. During this operation the least movement of the animal may cause a fatal laceration of the respiratory center. The attenuated end or needle of the instrument touches the bacilaire when the instrument is withdrawn. If the operation is properly done the animal suffers very little inconvenience. There is no convulsion or great disturbance of respiration. The prolonged point of the instrument touches the bone and prevents a fatal compression of the nervous tissue by the thicker part of the instrument. The animal is a little stunned for the moment, but rapidly recovers. In one or two hours sugar appears in the urine.

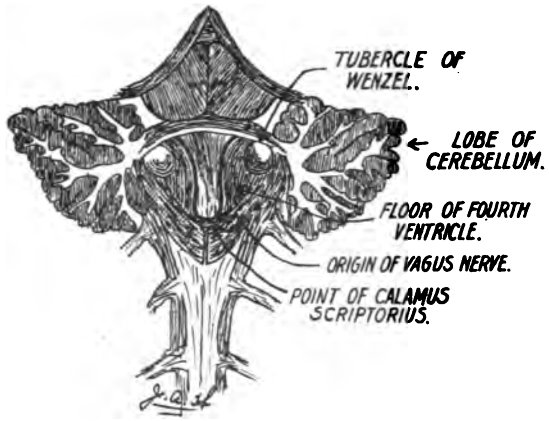


FIG. 49.—Showing the fourth ventricle of a rabbit. (After Bernard.)

Practice is necessary for this operation, and it may first be done on the dead animal and a postmortem performed to locate the site of the puncture. The second animal may be anesthetized, and if a dental drill or other suitable instrument is at hand the skull may be entered by that means. A very light hat-pin will suffice for the puncture needle.

Diuretic puncture: A similar puncture to that described, but slightly higher in the calamus results in a polyuria without glycosuria. This polyuria may last as long as forty-eight hours.

FERMENTS, ENZYMES AND DIGESTANTS.

All food is digested by ferments. Indigestion is one of the most common causes of sickness. It is natural to think, therefore, that the pharmacology of digestion or fermentation would be highly important; however, such is not the case. The study is full of interest, but of little value so far as the practice of medicine is concerned. Digestants are prescribed liberally, but are almost certainly useless, and the practice has fallen off much in recent years. Besides being prescribed as digestants, enzymes such as trypsin and papain have been injected into pathological tissues with the idea of digesting them, and so acting as caustics. The most important enzymes in pharmacology may be classified as follows:

1. Coagulating—thrombin and rennet.
2. Amidases—ptyalin and amylopsin.
3. Pepsin.
4. Trypsin.
5. Erepsin.
6. Catalases or those that liberate oxygen from hydrogen peroxide.

The general properties of these need not be rehearsed. We know nothing of their structure, as they are colloids of unknown composition, and as such are killed by heat, antiseptics, etc. When injected intravenously they produce toxic symptoms resembling albumoses and peptones; but this may be due to adhering albuminoid material. Powders like kaolin or charcoal when shaken with solutions of ferments absorb the ferment. In the same way, and perhaps to a greater extent, ferments are absorbed by the material upon which they act probably because of electrical attraction. (For a detailed account of enzymes, see Biochemical Catalysts in Life and Industry, Effront and Prescott, also Oppenheimer, Die Fermente.)

Experiment I.—In a series of test-tubes place 5 c.c. of milk, 5 c.c. of rennin and 5 c.c. of the following solutions:

1. Water.
2. Physiological saline.
3. Formaldehyde 1 to 1000.
4. Mercuric chloride 1 to 1000.
5. Pancreatin, 0.1 per cent.
6. Phenol, 1.1 per cent.
7. $AgNO_3$, 0.1 per cent.
8. KOH, 0.1 per cent.
9. HCl, 0.1 per cent.

Experiment II.—Repeat Experiment I, using 5 c.c. of 1 per cent. starch, 5 c.c. of saliva, diluted one-half and filtered, and 5 c.c. of the above solutions.

Experiment III.—Repeat Experiment I, using 5 c.c. of 1 per cent. trypsin, 5 grams of washed fibrin and 5 c.c. of the solutions in Experiment I.

Experiment IV.—Run about 10 c.c. of blood from an artery into 3 c.c. of the following solutions:

1. Water.
2. Liquor sodii chloridi physiologicus.
3. 5 per cent. peptone.
4. Saturated magnesium sulphate.
5. 1 per cent. potassium oxalate.
6. 1 per cent. hirudin.
7. 0.1 per cent. KOH.
8. 0.1 per cent. HCl.
9. 1 per cent. sodium citrate.
10. 1 per cent. sodium carbonate.

Discuss results in each case.

CHAPTER XXIII.

PHARMACOLOGY OF THE BLOOD.

Function.
Volume.
Relative Volumes of Corpuscles and Serum.
Viscosity.
Clotting.—Calcium, adrenalin, gelatin, hirudin, peptone, oxalates, fluorides, etc.
Alkalinity.
Acidosis.
Distribution in Tissues.
Drugs and Conditions Changing Volume and Distribution.
Laking.
Composition.
Sugar, content of.
Glycolysis.
Detoxicating, action of.
Blood-pressure; Muscle, nerves, heart.

FUNCTIONS OF THE BLOOD.

The Functions of the blood are:

1. To carry nutritive and energy-yielding material to the tissues.
2. To carry waste products from the tissues.
3. It is the medium of transmission of the internal secretions.
4. It aids in regulating the temperature of the body.
5. It carries oxygen from the lungs to the tissues and carbon dioxide from the tissues to the lungs, to the respiratory center and wherever needed.

These functions relate blood closely to every tissue in the body, and changes in the blood must modify the function of each tissue; but the physiology or pharmacology of the blood itself may be studied without reference to any other tissue.

To perform its functions normally, blood has certain qualities or properties and drugs may modify these, quantitatively only:

1. *Volume.*—The amount of blood in the vessels is normally one-thirteenth to one-fourteenth of the body weight, and serious

consequences follow any marked variation in the total volume or its distribution.

2. *Distribution.*—The distribution of this among the various organs in the rabbit is given by Ranke as follows:[1]

	Per cent.
Spleen	0.23
Brain and cord	1.24
Kidneys	1.63
Skin	2.10
Intestines	6.30
Bones	8.24
Heart, lungs, large vessels	22.76
Resting muscles	29.20
Liver	29.30

There is little occasion to attempt a *reduction* of the volume of the blood by drugs, though in cases of plethora it might be beneficial. As a matter of fact, however, it is not a very successful undertaking. Diaphoresis, diuresis, catharsis and the withholding of fluids from the food or drink may lessen the volume somewhat, but the object of such treatment is usually to remove toxins or other poisonous material or to favor the absorption of pleural, peritoneal exudates or edematous fluid rather than to reduce the volume of the blood primarily.

VOLUME OF THE BLOOD.

The volume may be increased by excessive drinking; the result, however, is very temporary. Anything that causes a dilation of the vessels, as the nitrites, may cause a very transient increase. Usually, however, the increase in volume is local, because drugs that dilate the vessels usually do so locally and not generally.

Increasing the volume of the blood is a more frequent and successful undertaking. After cases of severe hemorrhage a transfusion of blood is often made. Similarly, after operation or shock the blood-pressure may be raised by increasing the blood volume either by transfusion or by the injection of saline. In cases of chlorosis or anemias, iron and other drugs may increase the blood volume by increasing or building up red corpuscles. Hygienic and dietetic treatment may yield similar results.

VISCOSITY.

A certain viscosity seems necessary for blood to perform its proper function. If there be deficient colloidal matter to which the

[1] Howell, p. 458.

viscosity is due, the fluid tends to leave the vessels and to accumulate in the tissues. This is the cause of the relative failure of saline injection in cases of low blood-pressure due to shock or hemorrhage. It has been found in these cases, if saline alone be injected, that the rise in blood-pressure may be relatively short, because the fluid leaves the vessels either by way of the kidney or into the tissues to cause an edema. For this reason the addition of gum arabic or some other colloid, or the transfusion of blood, has been advocated.

Diminished viscosity also permits certain crystalloids like sugar to pass through the kidneys and perhaps also into the tissues. This can easily be shown by comparing the rate of dialysis in whole blood and serum. Sugar will dialyze from serum much more readily than from the whole blood.

Adrenalin and calcium salts increase the clotting of the blood and perhaps also its viscosity, while oxalates, potassium iodide and fluoride, organic substances, such as peptone, pepsin, snake venom or hirudin, lessen viscosity.

Anything that lessens the amount of protein in the blood or the volume of the corpuscles may lessen viscosity.

Normally, the protein of the blood is about 8 per cent. The volume of the corpuscles, however, is about one-half the total volume. Consequently, we should expect the blood to be of much greater viscosity than water.

The proteins are hydrophyllic colloids. Changes in acidity or alkalinity markedly modify the water-holding capacity of the proteins and consequently change the viscosity.

This viscid character is the most striking distinction of the organic and inorganic colloids. An 8 per cent. solution of blood has 4.4 to 5.5 times the viscosity of water. The viscosity of the blood is greater than serum, although the serum volume for volume contains almost twice as much protein as the blood, 60 to 39.

The viscosity bears a close relation to the number of corpuscles, as shown by the following table:[1]

Number of corpuscles per cubic millimeter.	Viscosity of serum plus corpuscles.
0	1.9
3.2 times 10^6	3.3
6.3 " 10^6	4.9
12.6 " 10^6	15.6

Increase in temperature reduces the viscosity, since at 37° it is 16 per cent. less than at 17°. An increase of 5° in fever

[1] Mathews: Physiological Chemistry, p. 512.

may reduce the viscosity 4 per cent. Increase in the hydrogen ion concentration of the blood increases the viscosity. Since CO_2 increases the hydrogen ion content, venous blood has a greater viscosity than arterial. Dyspnea increases it; hunger, salts, diminish it, while a meat diet increases viscosity. There are many conditions in the practice of medicine when the heart requires rest and relief from overwork and the viscosity of the blood is important, since the greater the viscosity the more work is placed on the heart to keep it circulating.

CLOTTING OF THE BLOOD.

Clotting is another mechanism for increasing the viscosity, but the phenomenon is so striking that it is generally considered by itself. However, the mechanism may be an extreme case of protein swelling due to absorption of water, such as occurs when an acid is added to gelatin. It is rendered more hydrophyllic, swells, and has a greater viscosity.

This is an important fundamental property of the blood, since if it were not present, everyone would be a hemophilic, or rather none would survive. It is a property essential to life. The real nature of it is not fully understood and probably will not be until we know more of the nature of matter.

It is generally accepted that the fibrin formed during the clotting is derived from fibrinogen. This substance can be prepared in solution free from other proteins.

The mechanism of the clotting has been presented by Howell in his *Physiology*. He prepares fibrinogen as follows:

Collect horses' or cats' blood by allowing it to escape from the vessel without coming in contact with the wounded surface or tissue into a solution of sodium oxalate of such strength that the final volume contains 0.1 per cent. oxalate.

Centrifuge and obtain clear plasma and add an equal volume of saturated sodium chloride. This precipitates fibrinogen, centrifuge and remove the supernatant liquid. Wash with a half-saturated solution of NaCl and then dissolve with stirring in a 2 per cent. solution of NaCl and filter. This is precipitated again by half-saturation with NaCl, centrifugalized, washed and the process repeated a third time, and the washed precipitate dissolved in a 1 per cent. solution of NaCl. It is sometimes necessary to add a few drops of a 0.5 per cent. solution of sodium bicarbonate to get this last precipitate into solution.

The solution so prepared will not clot except on the addition of blood serum containing the so-called fibrin ferment thrombin. If instead of thrombin Ca salts be added, and some sodium bicarbonate about the same concentration as in Ringer's solution, a clot may be formed, but very slowly.

This, Howell thinks, is due to the fibrinogen containing a trace of thrombinogen, the antecedent of thrombin.

Thrombin may be prepared as follows: Allow blood to clot, remove the serum and precipitate with 20 volumes of alcohol. let stand for a week and then filter. Dry the precipitate, grind it and extract it with water. The aqueous solution contains thrombin in addition to other proteins. A solution made in this way will cause the precipitation of fibrinogen. That thrombin is not present in normal blood, however, is shown by the fact that blood led directly from the artery into alcohol and extracted in the same manner as above will not yield a clot.

Calcium is necessary for normal clotting. This was shown by Arthus and Pages by adding sodium oxalate to plasma, so that the concentration was 0.1 per cent. It was then dialyzed until the excess of oxalate was removed. Dialyzed plasma will remain unclotted indefinitely, but clots immediately if a little calcium be added.

The role of calcium in clotting is in the conversion of prothrombin into thrombin, because it has been shown by Hammarsten that dialyzed oxalated plasma is readily clotted if some thrombin solution free from calcium be added to it.

The process of clotting may be represented as follows:

Ca + thrombinogen = thrombin.

Thrombin + fibrinogen = fibrin.

Since blood that comes in contact with tissues clots much more quickly than blood drawn without touching tissue, it is generally accepted that the tissues furnish an activator or kinase—thrombokinase that hastens clotting. To illustrate this properly the following formula is used:

Cellular elements = thrombokinase.

Thrombokinase + calcium + thrombinogen = thrombin.

Thrombin + fibrinogen = fibrin.

The pharmacology of clotting is concerned with any changes in the blood or its environment that alter the rate or nature of clotting.

Means of Hastening or Retarding Clotting.—Before all operations the clotting time is or should be determined. Normally, blood clots in from three to ten minutes. If for any reason clotting does not occur, or is long delayed, the operation may be contra-indicated.

Conditions Delaying or Preventing Clotting are: 1. *Low Temperature.*—This can best be shown with blood that normally is slow in coagulating. The blood of the horse, terrapin or birds coagulates slowly. If horse's blood be collected in narrow vessels surrounded by ice the clotting is so long delayed that the corpuscular elements, being of greater specific gravity than the plasma will sink gradually to the bottom and the clear yellow plasma can be pipetted off. Similarly, with the blood of all species, clotting is delayed, but in most cases coagulation even on cooling will be too rapid for the preparation of plasma.

2. *Coagulation is delayed by anything that precipitates or removes calcium as the oxalates or citrates.* These remove the calcium in insoluble form, and prevent the formation of the ferment necessary for clotting.

3. *Strong solutions of $MgSO_4$, and of Na_2SO_4 prevent clotting.* The explanation of this is not well understood, but it is believed to be due, in a measure, to their preventing the disintegration of the cellular elements, thus delaying or preventing the formation of thrombokinase. It is known that tissue products accelerate clotting and that blood within the veins does not readily clot. It may also be due to the precipitation of the calcium with these strong sulphate solutions. Similarly:

4. *Sodium Fluoride prevents clotting,* perhaps by precipitation of the calcium as fluorides. It may also lessen ferment action, and this would be an additional factor.

5. *Certain organic substances, like pepsin, trypsin, peptone and hirudin,* when injected, intravenously, prevent clotting. The mechanism of the action here is not understood, but it may be that these bodies cause an increase of antithrombin. Prevention of clotting is of use only in experimental work. It is never desired in medicine.

Agents Hastening Clotting.—Much more important than delaying clotting is the hastening of it. This cannot be done in the best way until we understand normal clotting. Since calcium is necessary for clotting, one of the first methods employed to hasten clotting is the administration of calcium salts. The value of these is questionable.

The intravenous injection of adrenalin also aids clotting. If this be given too quickly, however, there is danger from the increased blood-pressure.

Pressure to a bleeding surface aids coagulation, and the presence

of gauze, sponges, or clothes, or other bodies also aids. Pressure by causing the liberation of thrombokinase and acting as a foreign body furnishes a nucleus for the deposit of fibrin crystals, and also aid in the rupture of blood platelets, etc., and in this way hasten coagulation.

THE ALKALINITY OF THE BLOOD AND ACIDOSIS.

One of the essentials of life is an alkaline reaction. The actual alkalinity, while near neutrality, is yet insured against this actual neutrality by a reserve or potential alkalinity that is available in case of necessity.

An acid reaction is due to an excess of H ions; alkalinity is due to free OH ions. In water which is neutral in reaction, the $\overset{+}{H}$ and OH ions are in equal numbers, $\overset{+}{H}$ times $\overline{OH} = 10^{-14}$. The product of $\overset{+}{H}$ and $\overline{OH}$ in any dilute solution is always equal to this figure, consequently, when we know one we can calculate the other. An increase of H ions means a diminution of OH ions and *vice versa*.

Hydrogen Ion Concentration.—By this expression we mean the concentration of dissociated H, in terms of a normal solution. For example, if one gram of hydrogen is dissociated in 10,000,000 liters of water the concentration is 10^{-7} normal.

Method of Expressing H Ion Concentration.—It would obviously be cumbersome to express a dilution of one molecule of dissociated H in 10,000,000 liters of water by 0.0000001 and in biological work we are dealing mainly with these dilutions. A less cumbersome method of notation is therefore advisable. Consequently, the above dilution is written $H = 10^{-7}$. At the present time the custom is to use the logarithm only and to avoid the negative sign. The reciprocal 7 is used so that 10^7 really would mean 10^{-7}.

In order to save space and to express the concentration explicitly, Sörensen has suggested a plan which is very widely adopted. He expresses the potential or concentration of the H ions as PH_1, PH_2, PH_3, etc., where

$$
\begin{aligned}
PH_1 &= \tfrac{N}{10} \text{ acid or } H = 10^{-1} \\
PH_6 &= \tfrac{N}{1000000} \text{ acid or } H = 10^{-6} \\
PH_7 &= \text{Neutrally or } H = 10^{-7} \\
PH_8 &= \tfrac{N}{10000000} \text{ alkali or } H = 10^{-8} \\
PH_{13} &= \tfrac{N}{10} \text{ alkali or } H = 10^{-13} \\
PH_{14} &= \tfrac{N}{1} \text{ alkali or } H = 10^{-14}
\end{aligned}
$$

This system is brief, but confusing until studied. Since the numbers refer to negative logarithms the higher the number the fewer H ions in a given volume, while the OH ions increase. This is quite comprehensible when we remember that $\overset{+}{H}$ times OH is always 14 or 10^{-14}. If PH is 14, it follows that OH must be zero, and if PH_1 is $\frac{N}{10}$ acid P OH_1 must also be $\frac{N}{10}$ alkali. As now employed Sörensen's figures are the logarithms of the dilution in terms of normal solution.

PH_{14} is $\frac{N}{1}$ alkali, and when H is $PH_{13} = POH_1$ the solution is $\frac{N}{10}$ alkali.

Potential Alkalinity.—The weakly alkaline condition of the blood is guaranteed by a mixture of H_2CO_3, $NaHCO_3$ and NaH_2PO_4. These are all very weakly dissociating substances and may be considered in the blood to be in a balanced state:

$$\frac{H_2CO_3}{NaHCO_3} = K \text{ and } \frac{NaH_2PO_4}{N_2H\ PO_4} = K_2$$

When K and K_2 are constants and the sum of these constants in terms of H ions is about PH, 7.1 to 7.8 and may be briefly represented as:

$$\frac{H_2CO_3}{NaHCO_3} = K_1$$

If acid be added to this directly or indirectly, as in cases of acidosis, it liberates H_2CO_3. This will either break into CO_2 and H_2O and K, kept constant, or it will tend to act with Na_2CO_3 if such be present and restore the constant in that way. If enough acid be added or developed the whole alkali reserve may be exhausted. The phosphates are balanced in the same way. According to Michaelis and Garmendia the ratio of

$$\frac{NaH_2PO_4}{Na_2HPO_4} = \frac{1}{5.1} \text{ molecules.}$$

Since the normal blood always contains CO_2, $NaHCO_3$ and Na_2HPO_4 in this balanced state the H ion concentration at any one time cannot be determined by titration, because as fast as the actual alkalinity is removed the potential alkalinity is converted into actual. Consequently, the titration alkalinity is the sum of actual and potential.

This difference between the actual and total alkalinity of the blood is known as the "buffer" value and $NaHCO_3$ and $Na_2 HPO_4$ are the buffers, $NaHCO_3$ especially. The value of this buffer is illustrated by comparing the effect of acid added to a liter of water and to a liter of $NaHCO_3$. The reaction of a solution of pure $NaHCO_3$ is very weakly alkaline. Water is neutral. A drop of acid added to a liter of water will definitely acidify it. When added to a solution of $NaHCO_3$, however, it will not change the actual alkalinity and will not exceed the acidity of CO_2 until all of the $NaHCO_3$ has been decomposed. The amount of acid required to do this will depend on the amount of the $NaHCO_3$ in solution. In other words, on the buffer value of the solution. The carbonates are the chief biological buffers.

Acidosis. The actual significance of this term varies in many minds. As generally accepted, a state of acidosis exists when large amounts of acetone, aceto-acetic acid, and in the more severe cases, β-oxybutyric acid, are excreted in the urine. This occurs frequently in diabetes. The actual alkalinity of the blood may not be changed for a long time, but these bodies as they are excreted combine with and exhaust the reserve alkalinity or buffer alkalinity.

Normal adults excrete 3 to 15 mg. of combined acetone and aceto-acetic acid per day. Over 20 mg. is considered pathological. The amount may be increased by fasting, and by and by an exclusively carbohydrate diet, diabetes, intoxications of pregnancy and other diseases may cause an abnormal amount to develop.

SPECIFIC GRAVITY OF BLOOD.

The specific gravity of the blood has so far been no aid in diagnosis. Normally it varies between 1.045 to 1.075. The simplest method of determining the specific gravity is that of Hammerschlag, which consists of mixing $CHCl_3$, specific gravity 1.526, and benzol, specific gravity 0.090, until the mixture has the specific gravity of about 1.055 as determined by a spindle. A drop of the blood is then dropped in, and if it sinks $CHCl_3$ is added, and if it rises to the top, benzene is added until the gravity of the blood is obtained, when the blood will float without any marked tendency to rise or fall. The specific gravity of the mixture is then determined. The action of drugs on the specific gravity is very slight.

Laking or Hemolysis.—Hemolysis, or the discharge of hemoglobin from the corpuscle, is important in pharmacology, because by a knowledge of its causative agents one may avoid serious accidents,

and because many drugs and diseases may cause laking and hemoglobinuria. *The agents that may cause laking are:*

1. Water or hypotonic solutions intravenously.
2. Ether, chloroform or alcohol.
3. Soaps and fatty acids.
4. Blood from a different species, and in some cases of transfusion hemolysis.
5. Bile and bile salts.
6. Certain drugs, as $KClO_3$, saponins, gallic acid, sapotoxins, alkalies and solanin.
7. Toxins of bacteria and snake venom.
8. Exposure to cold may cause some laking, especially alternate freezing and thawing.

The direct harmful effect is disturbance of oxidation, metabolism, injury to kidneys, heart or central nervous system either from anemia or the products liberated by the destruction of hemoglobin.

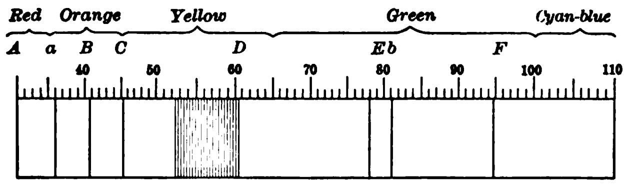


FIG. 50.—Spectrum of hematin in alkaline solution. (v. Jaksch)

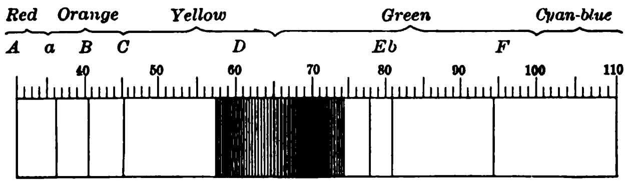


FIG. 51.—Spectrum of reduced hemoglobin. (v. Jaksch.)

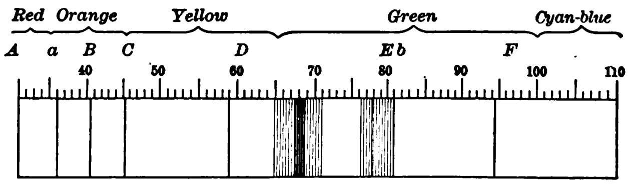


FIG. 52.—Spectrum of reduced hematin. (v. Jaksch.)

Nature, Amount, and Changes in the Hemoglobin.—The hemoglobin is exceedingly important in pharmacology because it is the direct

oxygen carrier of the body and because it forms compounds very readily with many gases. Its amount and functions are also varied and modified in many diseases.

Hemoglobin is a conjugated protein. It may be broken up by heat, acid, or by alkalies into a protein, globin, and a pigment, hematin. The hematin is about 5 per cent. of the whole molecule. Hemoglobin is therefore a compound of a protein and hematin. The composition of the molecule varies in different animals. Dogs' hemoglobin, according to Jaquet, is about $C_{758}H_{1203}N_{195}S_3FeO_5$. Globin is levorotary while hemoglobin is dextrorotary. In man the amount of hemoglobin is about 14 percent. of the blood weight. The amount varies under different conditions and the determination of the amount of hemoglobin is a routine clinical procedure. There are numerous instruments devised for the purpose.

Experiment I.—*Coagulation.*—Anything that precipitates the calcium of the blood will delay clotting. Arrange a series of test-tubes, properly labelled. Collect for control 10 c.c. of blood and note the clotting time.

(*a*) Add 1 c.c. of NaCl solution and save this also for control. Note clotting time in every case.
(*b*) Add 1 c.c. of K Fl. solution.
(*c*) Add 1 c.c. of sodium citrate solution.
(*d*) Add 1 c.c. of an oxalate solution.
(*e*) Add 1 c.c. of magnesium sulphate solution.
(*f*) Add 1 c.c. of peptone solution.
(*g*) Add 1 c.c. of 1 to 1000 adrenalin.

Experiment II.—Having determined the clotting time of the blood, inject several times 0.5 c.c. of $\frac{1}{1000}$ epinephrin solution, and after ten minutes again determine the clotting time. After this has changed inject slowly into the vein 5 grams of peptone in solution. After fifteen minutes again determine the clotting time. Note the difference in the effect of peptone when added to shed blood and when injected into the circulation.

Experiment III.—*Viscosity.*—KI increases the fluidity of the blood and therefore lessens the viscosity. CO_2 increases the viscosity. These are perhaps not sufficiently appreciated. When the heart is overworked any decrease in the CO_2 will lessen the work by lessening the viscosity. KI may have the same effect.

Arrange a three-way cannula with a very small outlet so that the blood drops from it sufficiently slow to be counted. Insert in a vein and count for several times. If clotting takes place wash out. When an average of the drops per minute has been found, asphyxiate

the animal and again determine. Allow to return to the normal and administer 1 or 2 grams of KI intravenously and again determine rate of flow. This will give an idea how the viscosity may be determined. There are many sources of errors. (See Dunstan and Thole[1] for the methods of determining the viscosity of colloids.)

Alkalinity and Acidity Changes of the Blood.—Study the titratable and actual acidity of the blood and the meaning of each. Assign a review of Fischer's theory of edema and its importance in this respect. Also some of the criticisms of the theory.

Experiment IV.—Hemolysis or Laking.—Put a little fresh blood in each of three test-tubes. Dilute with one, two and three volumes of water. Hold over a printed page immediately and note the opacity. In a few minutes laking will occur and the print can be read through the liquid. Laking will also occur if bile salts, chloroform, dilute acetic acid, in 0.9 per cent. NaCl, ether, saponin, etc., are used. Foreign sera and toxins also cause laking.

Experiment V.—Osmotic Resistance of the Corpuscle.—*Fragility of the Corpuscle.*—This shows why water cannot be injected into the circulation without injury or death of the animal. Arrange a series of ten test-tubes. In the first put 6 c.c. of 1 per cent. NaCl, in the next 5.8 c.c., in the third 5.6 c.c. and so on, each differing from the preceding by 0.2 c.c. Now add sufficient water to each to make the volume in each 10 c.c. This is done by adding 4 c.c. to the first, 4.2 c.c. to the second and so on. Both salt solution and water should be measured from accurate burettes. Put into each tube 1 c.c. of fresh blood, shake moderately until mixed and allow it to stand from ten to thirty minutes. Observe the color of the clear liquid in the tubes above the sediment. Determine in which tube the first tinge of hemoglobin appears. This method is used clinically to determine the fragility of the corpuscle.

Crenation.—This is the opposite of laking. Add 5 per cent. of NaCl to the blood and examine under the microscope.

Experiment VI.—Changes in the Oxygen Carrying Power of the Blood; Toxicology.—Examine a dilute solution of normal blood with the spectroscope and locate absorption bands.

Carbon Monoxide Hemoglobin.—Pass coal gas or CO through blood for a considerable time and again examine.

Methemaglobin.—Add a few drops of a strong solution of potassium ferricyanide to blood in a test-tube and heat gently. The color changes to a chocolate tint. A distinct band is seen on the

[1] The Viscosity of Liquids.

red side of the D line. (See Beddard, *Practical Physiology*.) On addition of ammonium sulphide this band disappears. The oxyhemoglobin bands are seen for a moment and then give place to the band of reduced hemoglobin (*q. v.*).

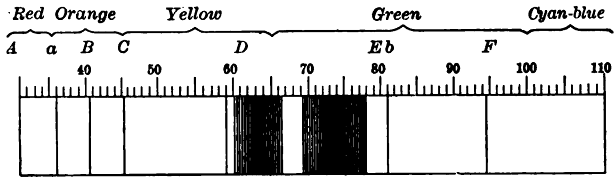


FIG. 53.—Spectrum of oxyhemoglobin. (v. Jaksch.)

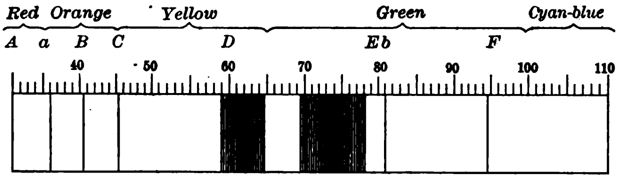


FIG. 54.—Spectrum of carbon monoxide hemoglobin. (v. Jaksch.)

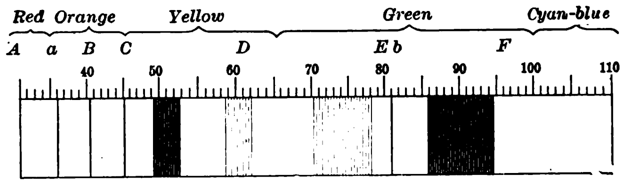


FIG. 55.—Spectrum of methemoglobin in acid and neutral solutions. (v. Jaksch.)

Cyanhemoglobin.—The blood after poisoning with cyanides is of a bright red color—cyanhemoglobin? It is easily formed by adding HCN to an alkaline solution of hematin or to a solution of methemoglobin. It has an absorption spectrum very similar to reduced hemoglobin. Cyanhemoglobin is a combination of methemoglobin with cyanide. A very delicate test for cyanide is: Form methemoglobin by adding a little amyl nitrite or $KClO_3$ to blood. Place a little of this on a filter paper. If a trace of cyanide be added to one point and allowed to dry the paper at this point instead of being chocolate brown will be bright red.

Hematoporphyrin.—This is present in small amounts in normal urine. It has a different absorption band in acid and alkaline solutions. It may occur especially after the use of sulphones. In such cases the urine is dark red. It is perhaps isomeric with bilirubin and gives a play of colors when treated with fuming nitric acid.

Permeability of the Red Corpuscle.—Ether, esters, aldehyde, and acetone divide in the blood so that the corpuscle contains more than the serum. Monatomic alcohols divide equally between serum and corpuscle, diatomic alcohol-glycol about equally. Triatomic and tetratomic alcohols penetrate the corpuscle less readily while there is little sugar in the corpuscles. Pentatomic and hexatomic pass in with great difficulty.

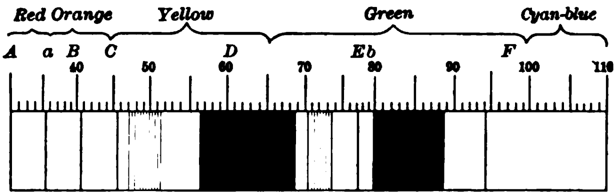


FIG. 56.—Spectrum of hematoporphyrin in alkaline solution.

The Presence of Drugs in the Blood.—It is perhaps safe to say that only those drugs that act directly on the blood—like CO_2, O_2, etc.—remain for any length of time in the blood. Strychnin, for example, soon leaves the blood and is found mainly in the nervous system; formaldehyde if introduced into the blood soon disappears by oxidation or otherwise.

Drugs which are not decomposed in the body wander in and out of the blood in absorption and excretion; but only a small concentration is found in the blood at any one time. In many cases this small amount is hard to detect.

Experiment I.—Anesthetize a dog with ether. Record respiration and blood-pressure. Insert a cannula into the femoral vein for injection of solutions and a cannula into the carotid artery to take the blood samples for analysis. Inject 10 c.c. formaldehyde (about 6 per cent.) slowly into the vein. When the blood-pressure is at the lowest point withdraw 25 c.c. of blood, acidify with phosphoric acid and distil with steam. Test the first 20 c.c. of the distillate for formaldehyde as follows:

Hehner's Test.—Mix 5 c.c. of the distillate with 5 c.c. of milk (skim milk); add an equal volume of concentrated sulphuric acid, containing a mere trace of iron (about 1 c.c. of 1 per cent. Fe_2Cl_6 per liter); add the sulphuric acid carefully so that it does not mix with the milk but forms a layer under the solution to be tested. At the junction of the liquids a violet or blue color will appear if the milk solution contains more than 1 to 10,000 formaldehyde.

Rimini's Test as Modified by Schryver.—To 10 c.c. of the distillate to be tested add 2 c.c. of a freshly prepared filtered 15 per cent. solution of phenylhydrazin hydrochloride. Then 1 c.c. of freshly prepared 5 per cent. sodium ferricyanide and 5 c.c. of hydrochloric acid. A brilliant magenta color is produced. The test is sensitive up to 1 part of formaldehyde in 100,000.

In ten minutes again, after taking the first sample of blood, take 25 c.c. of blood and again test for the presence of formaldehyde. If it is still present repeat again in fifteen minutes.

Collect urine at the end of the experiment and test either directly or after the distillation as in case of the blood.

Experiment II.—In a second animal, or the animal used for formaldehyde after the blood no longer shows the presence of the drug, inject 2 grams of hexamethylamin in 50 c.c. of normal saline solution. Test the blood immediately after the injection and every fifteen minutes thereafter for four times or until the blood shows no formalin test. At the conclusion of the experiment test the urine for formaldehyde.

Experiment III.—Give a dog 1 gram of sodium salicylate by mouth in solution or in a capsule (preferably in solution). Every thirty minutes withdraw 20 c.c. of blood and test for salicylates as follows: Dilute with 50 c.c. of water, acidify with dilute acetic acid and add 10 grams of sodium sulphate, then boil and filter. To 5 c.c. of the filtrate add a drop of ferric chloride; a bluish purple color indicates salicylic acid. Since the sodium salicylate in the blood is decomposed on acidifying into salicylic acid which is insoluble, and may be removed by the clot on filtering, this rough test may not show the presence of salicylate even when it is present in the blood.

A direct shaking of the blood with ether or chloroform is not good because of laking and solution of hemoglobin in the solvent. In such cases the following method is recommended: Take 25 c.c. of blood and dilute to 100 c.c. with water. Place in a short-necked flask, one and a quarter inches in diameter, acidify with phosphoric acid and distil with steam. The distillation of the salicylic acid is facilitated by submerging the flask in an oil bath at a temperature of from 120° to 130° C., and leading a current of steam through it, or by adding 20 grams of sodium chloride to the blood solution to raise the boiling-point. Do not char the blood by direct heat. Test the distillate direct with ferric chloride or shake the distillate with ether; evaporate the ether and test the residue.

CARBON DIOXIDE.

Experiment I.—Anesthetize a dog with ether and prepare for blood-pressure and respiratory tracings. Administer CO_2 from a nitrous oxide apparatus. Study especially the action on the blood-pressure. Alternate with O_2.

Experiment II.—Remove the mask and allow the animal to return to normal. Now shut off the trachea with a clamp and take a tracing until the animal shows signs of impending death; then remove the clamp and resuscitate.

Experiment III.—Give curara until the respiratory muscles are paralyzed. Insert a tracheal catheter for intratracheal insufflation. Alternate with oxygen and carbon dioxide and observe the effect on the heart.

Experiment IV.—Solid carbonic acid (carbonic acid snow) has been used as an irritant in chronic inflammatory conditions also as a local anesthetic, due to its freezing powers. It is also used for the preparation of histological sections.

LEWIS-BENEDICT METHOD OF DETERMINING BLOOD SUGAR.

Dissolve 36 grams of picric acid in 50 c.c. of 1 per cent. NaOH. Cool and dilute to 1000 c.c. Take 2 c.c. of blood and wash out into a test-tube with 4 c.c. water to lake. When laking is complete make up to 25 c.c. with the picrate solution. Shake and filter. Measure 8 c.c. into a tube graduated at 12.5 c.c. and 25 c.c. Add 1 c.c. of 20 per cent. Na_2CO_3 and heat in a water-bath for fifteen minutes. Compare the color of this solution by means of a colorimeter with that of a 0.1 per cent. solution of dextrose in picrate solution which has been treated in exactly the same way as the blood. It makes little difference what volume of blood is taken provided the same volume of the standard solution is taken. The volumes given in the original method are for convenience in calculation where a permanent standard is used. I believe the better method is to make the standard new with each determination.[1]

PHLORIDZIN.

Experiment I.—Dissolve 0.25 gram of phloridzin in 4 c.c. of olive oil and inject subcutaneously into a rabbit. Collect the urine with a catheter every thirty minutes and test for sugar.

[1] Jour. Biol. Chem., 1915, xx, 61; ibid., 1919, xxxvii, 503.

Experiment II.—Give a rabbit 2 c.c. of epinephrin, 1 to 1000 hypodermically. Collect the urine and test as in Experiment I.

Experiment III.—Take a sample of blood from a dog and determine the amount of sugar by the Benedict method. Dissolve 1 gram of phloridzin in 7 or 8 c.c. of olive oil and inject subcutaneously or intraperitoneally. Collect the urine every two hours and test for sugar. When sugar appears, determine the amount and also the amount in the blood at the same time.

Experiment IV.—Determine the blood-sugar in a dog's blood. Give it a hypodermic of 2 c.c. of epinephrin every fifteen minutes for five times. Collect the urine at the end of two hours. Detêrmine the amount of sugar in the blood and compare with the phloridzin animal.

SAPONINS.

From a chemical standpoint most saponins are non-nitrogenous glucosides, but because of some striking physical actions in which they resemble soap they are called saponins. They foam when shaken in water and emulsify fats. They are not absorbed from the intact alimentary canal, but have a local irritating action. In small doses they are expectorants. Quillija, senega root and sarsaparilla owe their action to saponins. They are little used for this purpose and have a very limited use in medicine. If a solution of saponin is added to blood or injected into the circulation it causes a laking of the red corpuscles with free hemoglobin in the serum and urine. The laking is due to changes in the corpuscular envelope. The most toxic saponins are called sapotoxins.

Experiment I.—Shake a few drops of tincture of soap bark with a little water. Note results. Add about 2 c.c. tincture of soap bark to about 1 inch of cottonseed oil in a test-tube and shake. Result? What is emulsification?

Experiment II.—Shake a solution of saponin in water. Study the relation of saponin to surface tension by placing a little sulphur in water and comparing the effect with sulphur dusted on a 1 per cent. saponin solution. How would you detect saponin in plant extracts?

Experiment III.—Laking of blood by saponin.

(*a*) To 5 c.c. of blood add 0.5 c.c. of 3 per cent. saponin solution in 0.9 per cent. NaCl.

(*b*) As a control use 0.5 c.c. of 0.9 per cent. NaCl solution. Keep the mixtures at 40° C. Laking soon occurs in the saponin solution.

Experiment IV.—Cholesterin neutralizes the action of saponin. Prepare test-tubes as follows:

1. Five c.c. of 0.9 per cent. NaCl.
2. Five c.c. of 0.9 per cent. NaCl, containing 0.5 c.c. of 3 per cent. saponin.
3. Same as 2, but in addition add 0.2 of 1 per cent. solution of cholesterin in ether.
4. Five c.c. of blood plus 0.2 c.c. cholesterin in ether.
5. Five c.c. of distilled water.

To each tube add 0.25 c.c. defibrinated blood and set in an incubator at 40° C. Observe in fifteen and thirty minutes. Which tubes can you read printed matter through?

Experiment V.—Taste a 0.1 per cent. solution of saponin. Do not swallow more than 1 c.c.

Experiment VI.—In the following experiments record changes in heart-rate, respiration and general symptoms. Give by mouth to a dog 10 c.c. of 0.1 per cent. solution of saponin per kilogram body weight. Note and record symptoms.

Experiment VII.—Give a dog 2 c.c. per kilo of 0.1 per cent. solution of saponin hypodermically.

Experiment VIII.—Give a dog 1 c.c. per kilo of 0.1 per cent. saponin intravenously.

Experiment IX.—Take a tracing of a frog or turtle heart and perfuse or irrigate it with 0.01 per cent. saponin in 0.8 per cent. NaCl. Compare result with digitalis.

LIST OF STOCK SOLUTIONS.

These solutions are kept for convenience and may be diluted when needed. They should be made up in 0.8 per cent. NaCl or in Ringer's solution.

Adrenalin hydrochloride or other epinephrin solution, 1 to 1000. It is preferable to purchase this in tablet form of such strength that one tablet in 1 c.c. will make a 1 to 1000 solution.

Aconitin, 0.1 per cent., also the tincture.

Alcohol, various solutions	1 to 80 per cent.
Amyl nitrite	1 per cent. and in 3 minim and 5 minim pearls.
Atropin	0.1 and 1 per cent.
Acacia	6 per cent. freshly made.
Barium chloride	0.01, 0.1, 1 per cent.
Caffein	0.1, 0.5, 1, 2 per cent.
Caffein citrate	0.1, 0.5, 1, 2 per cent.
Caffein sodio-benzoate	0.1, 0.5, 2 per cent.
Calcium chloride	0.1, 0.3, 0.5, 1 per cent.
Carbolic acid	0.5, 1, 5 per cent.

Chloral hydrate	0.1, 1, 2 per cent.
Chloroform	0.05, 0.1, 0.5 per cent.
Cocaine, HCl	0.01, 0.2, 0.5, 1 per cent.
Codeine phosphate	0.5, 1 per cent.
Curara	0.5, 1 per cent., slightly acidify with $\frac{N}{10}$ HCl.
Digitalis	0.0005, 0.001, 0.002, 0.1, 0.5 per cent., also the tincture.
Ergot, fluidextract, dilute as needed.	
Ether	1, 2, 5 per cent.
Hyoscyamin	1 per cent. of the hydrochloride and the hydrobromide, also the tincture.
Morphin sulphate	0.3 per cent. make up as needed.
Nicotin	0.1, 1 per cent. with a little $\frac{N}{10}$ HCl dilute as needed.
Nitroglycerin	0.1 per cent.
Physostigmin or physostigmin salicylate	0.1 and 1 per cent.
Pilocarpin nitrate	0.1, 1 per cent.
Potassium chloride	0.03, 0.1, 5 per cent.
Potassium bromide	0.03, 0.1, 5 per cent.
Quinine, HCl	0.1, 1 per cent.
Quinine bisulphate	0.1, 1 per cent.
Sodium nitrate	0.01, 0.05, 1 per cent.
Sodium sulphate	1, 10 per cent.
Strychnin, nitrate or sulphate	0.01, 0.1, 1 per cent.
Thebain	0.5, 1 per cent.
Veratrin	0.05, 1 per cent.

INDEX.

NAME	DATE DUE
Kenneth L. Gardner	MAY 23 '24
H. McCurdy.	JUN 1 1925
~~[illegible]~~	OCT 10 '25
L. M. Bayer	
Joe [illegible]	MAR 25 '26
	AUG 23 '27
J. Louis Freedman	APR 15 '30